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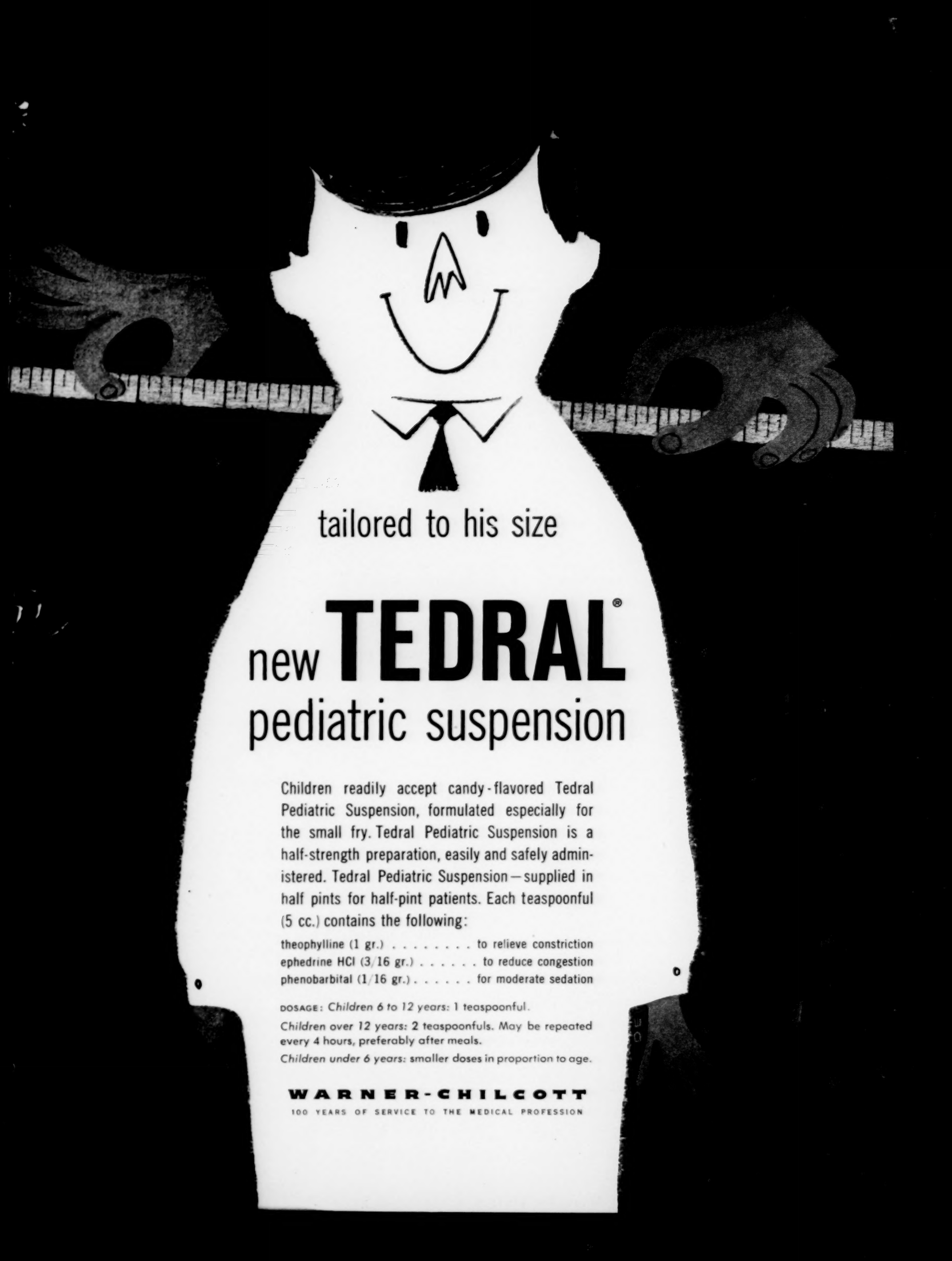
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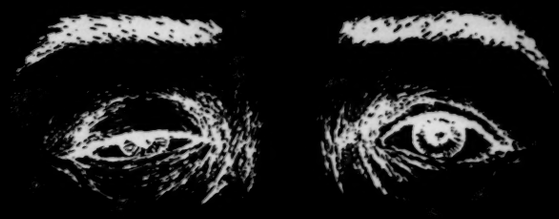
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1. Schwab, R.S.; Marshall, Clare K.; and Timberlake, William: *J.A.M.A.*, 158:625, June 25, 1955.
2. Schwab, R.S.: *Am. Jour. Med.*, 19:734, Nov., 1955.

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The American Journal of Medicine

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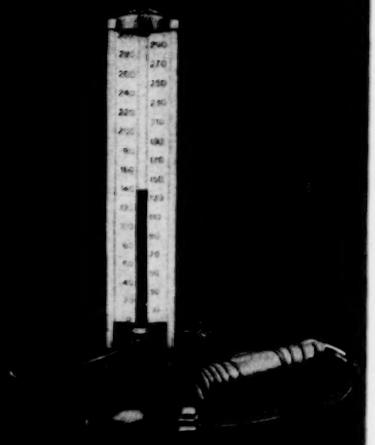
Clinical Studies

Thrombotic Thrombocytopenic Purpura. A Report of Three Cases J. George Sharnoff 740

This interesting report on an obscure disorder of controversial pathogenesis emphasizes the possible role of bone marrow stimulation, with release of cellular elements including megakaryocytes and platelets into the circulation, and consequent thrombosis. Primary vascular changes were not observed. In view of the occurrence of pulmonary megakaryocytosis and apparently also of similar throm botic lesions in the leukemias (with which thrombotic thrombocytopenic purpura appears to have some affinities in the author's view) it is suggested that the disorder may not be a disease sui generis.

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VOLUME TWENTY-THREE NUMBER FIVE

The Appearance of New Cardiac Murmurs in Patients Having Rheumatic Heart Disease with No Concomitant Evidence of Rheumatic Activity
T. N. HARRIS, SIDNEY FRIEDMAN AND JAMES TANG 748

The authors have carefully documented the fact, doubtless appreciated by most students of the disease, that there are degrees of rheumatic activity so subtle and insidious as to give no clinical or laboratory indication of extension of cardiac involvement, irrespective of whether the activity is continuously or intermittently progressive. Four cases of such occult advance of the disease are cited in patients who appeared clinically to be quiescent and in whom measurements of acute phase reactants and antibodies to streptococcal antigens remained within the normal range throughout. Other variants in the natural history of progressive rheumatic disease, similarly studied, gave comparable results.

The Accuracy of Diagnosis of Myocardial Infarction. A Clinicopathologic Study
BRUCE C. PATON 761

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Seminar on Atherosclerosis

Hormonal Influences on the Serum Lipids . . . . . DAVID ADLERSBERG 769

Dr. Adlersberg puts into perspective the very large literature on the influence of the various hormones on the serum lipids, adding data of his own. The thyroid is first considered, including the effects of thyroxine analogs which have comparatively little calorigenic action but are capable of reducing the serum cholesterol. Then gonadal influences are discussed, and application of estrogenic compounds to modify serum lipid levels. An account of the influence of adrenals, pancreas and pituitary follows, both in experimental animals and in man. Throughout the emphasis is not only on physiological regulation of lipid metabolism but also on possible application to the prevention of atherosclerosis and related disturbances in lipids.

Case Reports

Studies of Potassium Secretion in Glomerulonephritis
MILTON E. RUBINI, JAY P. SANFORD AND WILLIAM H. MERONEY 790

An interesting report of a case of probable glomerulonephritis with hyperkalemia disproportionate to the impairment of glomerular filtration, suggesting defective tubular secretion of potassium.

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VOLUME TWENTY-THREE NUMBER FIVE

"Cor Triatriatum"
C. Glenn Sawyer, Robert S. Pool, Walter C. Beck and Louis B. Daniel, Jr. 798

A well described case of a rather rare anomaly which hemodynamically simulates mitral stenosis but, as the authors point out, could be suspected by cardiac catheterization studies. The condition should be amenable to surgical correction.

Comparison of Serum Phosphohexose Isomerase Activity and Urinary Calcium Excretion in a Patient with Metastatic Mammary Carcinoma
W. P. Laird Myers and Oscar Bodansky 804

A case illustrating the expanding use of measurements of specific enzyme activities in the serum, in this instance serum phosphohexose isomerase in a patient with metastatic carcinoma of the breast, for early detection of disease states.

Chronic Systemic Melioidosis. Review of Literature and Report of a Case, with a Note on Visual Disturbance Due to Chloramphenicol
Amos L. Prevatt and John S. Hunt 810

An instructive case of Malleomyces pseudomallei infection. As the authors indicate, the disease may well originate in sites not now generally recognized as areas of infection, and it is to be hoped that this report will increase awareness of this possibility.

Hageman Trait (Hageman Factor Deficiency). Robert T. S. Jim and Sam Goldfein 824

A well studied example of an uncommon deficiency resulting in a coagulation defect which, curiously, usually is not associated with any bleeding tendency.

Resuscitation from Cardiac Arrest Due to Digitalis by External Electric Stimulation
Paul M. Zoll, Arthur J. Linenthal and Jason E. Lucas 832

An interesting case of cardiac syncope due to digitalis intoxication, in which external electric stimulation of the heart was successfully employed for resuscitation.

Post-transfusion Thrombocytopenic Purpura . . . . . Francis W. Michel 838

A significant report. The sudden and unexpected development of thrombocytopenic purpura after transfusion in a patient previously free of any such complaint led to investigation of the donors after the usual causes had been excluded. One donor, who had sarcoidosis, which may be relevant, was found to have potent platelet agglutinins in his (apparently compatible) blood.

Advertising Index on Page 103

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Number of patients	173
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Average weekly weight loss	2-2½ lbs.
Side effects	9*

*Minimized by dosage adjustment

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Number of patients	52
Average daily dose	2-3 tablets (5 mg. each)
Average duration of treatment	9 weeks
Average weekly weight loss	2.1 lbs.
Side effects	1*

*Adjusted with dosage

economy and low dosage of LEVONOR make it possible to administer this drug long enough to favorably alter the patient's eating habits.

Administration and Dosage:

Average dose: 5 to 10 mg. twice daily.

Bibliography

1. Sc. Exhibit, N. Y. State Med. Meeting, Feb. 18-21, 1957.
2. Pomeranze, J.: Report 807: 1957.
3. Frohman, I. P.: Report 315: 1957.
4. Dwyer, Thomas: Report 912: 1957.
5. Gadek, R. J.: Report 186: 1957.
6. Sc. Exhibit, Mich. State Med. Soc. Meeting Sept. 25-27, 1957.

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during pregnancy
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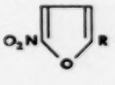
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Oral Suspension, 25 mg. per 5 cc. tsp., bottle of 60 cc.
(Readily miscible with water, milk or fruit juices.)

REFERENCES: 1. Nesbitt, R. E. L., Jr., and Young, J. E.: Obst. Gyn., N. Y. 10:89, 1957. 2. Diggs, E. S.; Prevost, E. C., and Valderas, J. G.: Am. J. Obst. 71:399, 1956. 3. MacLeod, P. F.; Rogers, G. S., and Anzlowar, B. R.: Internat. Rec. Med. 169:561, 1956.

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Lewis, H. H.: Frumess, G. M., and Henschel, E. J.: Rocky Mountain M. J. 54:806 (Aug.) 1957.

"Results of treatment with oleandomycin-tetracycline of 50 infections [mostly respiratory] due to resistant organisms and 40 infections [respiratory, skin, urinary infections] due to sensitive organisms are very encouraging. In some of these patients, [Signemycin] was lifesaving, and in others surgery was made unnecessary. This confirms other reports."

Shubin, H.: Antibiotic Med. & Clin. Therapy 4:174 (March) 1957.

Based on case reports documented by independent investigators in 26 countries abroad, the clinical response obtained with Signemycin in 1404 patients with a wide variety of infections was successful in 1329 patients; in 13 cases only was it necessary to discontinue therapy because of side effects.

Report on 1404 Cases Treated with Signemycin: Medical Department, Pfizer International. Available on request.

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Levi, W. M., and Kredel, F. E.: J. South Carolina M. A. 53:178 (May) 1957.

Of 50 patients with various infectious processes, 26 had not responded to previous antibiotic therapy. With Signemycin "Ninety-six per cent of the mixed infections were clinically controlled. . . . and in none of the cases was there any reason to discontinue the drug."

Winton, S. S., and Chesrow, E.: Antibiotics Annual 1956-1957, New York, Medical Encyclopedia, Inc., 1957, p. 55.

Signemycin in 79 patients with severe soft tissue infections: "The average response of these cases was excellent and inflammatory symptoms subsided with almost uniform rapidity....The magnitude and incidence of surgical intervention was reduced....Side reactions were minimal. . . ."

LaCaille, R. A., and Prigot, A.: Antibiotics Annual 1956-1957, New York, Medical Encyclopedia, Inc., 1957, p. 67.

Five groups of patients (total 211) with acne were treated with one of five antibiotic agents, including Signemycin (55 cases). "The results were evaluated taking into consideration the usual response to such conservative conventional therapy and the rapidity of response." In 8 weeks, Signemycin rapidly attained and maintained the highest percentage of efficacy of antibiotic agents tried.

Frank, L., and Stritzler, C.: Antibiotic Med. & Clin. Therapy 4:419 (July) 1957.

In the treatment of 78 patients with tropical infections, some complicated by multiple bacterial contamination or present for years, Signemycin was found to be "...an exceptionally effective agent," requiring smaller doses and less extended periods of therapy than with the tetracyclines alone, and "caused no notable toxic reactions."

Loughlin, E. H., and Mullin, W. G.: Antibiotics Annual 1956-1957, New York, Medical Encyclopedia, Inc., 1957, p. 63.

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References: 1. Gerzon, E. P., McCormick, T. H., and Konigsberg, S.: Am. J. Digest. Dis. 1:555, 1956. 2. Holt, J. O. S., Jr.: Dallas M. J. 42:497, 1956. 3. Applezweig, A. L.: Am. Pract. & Digest Treat. 7:1456, 1956. 4. Council on Pharmacy and Chemistry: New and Nonofficial Remedies, J.A.M.A. 163:76, Sept. 1, 1957.

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*Garrett, T. A.: Clinical Medicine 3: 1185 (Dec.) 1956

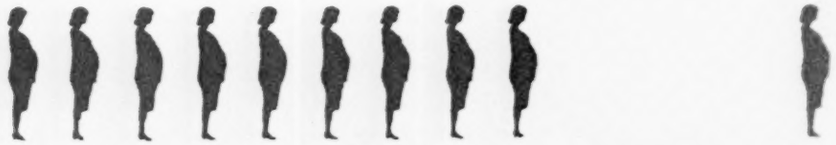
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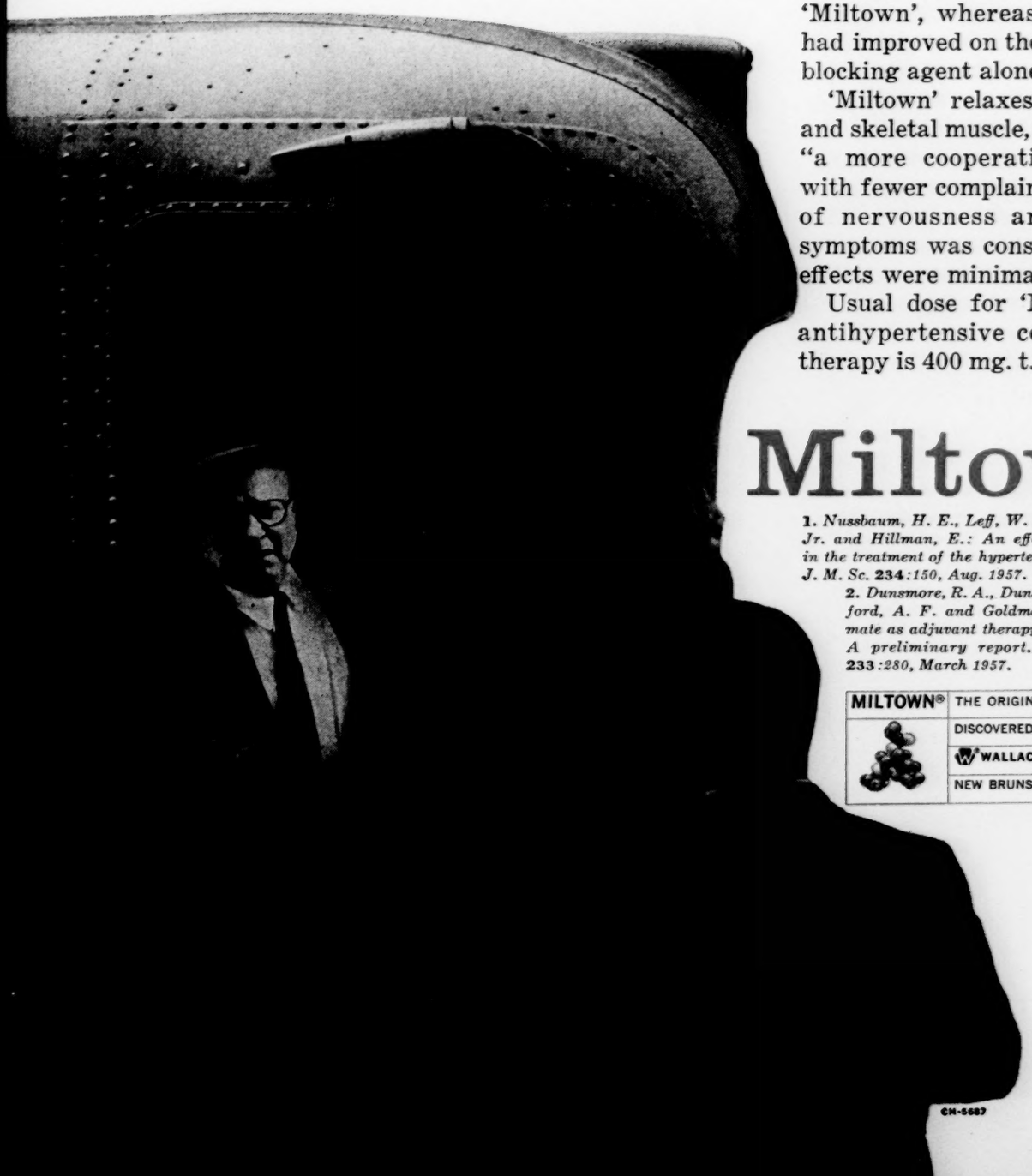
†due to calcium-phosphorus imbalance.

*Goldsmith, J. W.: Minn. Med. *40*:99 (Feb.) 1957.

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PSYCHIC pressure is blood pressure's twin. Many aggravating symptoms in hypertension are due to anxiety and tension.

Hypertension can be managed more successfully when *mental* pressure and *blood* pressure are treated together. Both objective and subjective over-all improvement was recorded in 95% of hypertensive patients receiving ganglionic blocking therapy in combination with 'Miltown', whereas only 76% had improved on the ganglionic blocking agent alone.[1]

'Miltown' relaxes *both* mind and skeletal muscle, and creates "a more cooperative patient with fewer complaints."[1] Relief of nervousness and anxiety symptoms was consistent; side effects were minimal.[2]

Usual dose for 'Miltown' in antihypertensive combination therapy is 400 mg. t.i.d. or q.i.d.

Miltown®

1. *Nussbaum, H. E., Leff, W. A., Mattia, V. D., Jr. and Hillman, E.: An effective combination in the treatment of the hypertensive patient. Am. J. M. Sc.* **234**:*150, Aug. 1957.*

2. *Dunsmore, R. A., Dunsmore, L. D., Bickford, A. F. and Goldman, A.: Meprobamate as adjuvant therapy in hypertension: A preliminary report. Am. J. M. Sc.* **233**:*280, March 1957.*

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supplied Pink, enteric coated tablets (250 mg.), bottles of 36. Yellow, scored tablets (250 mg.), bottles of 50.

references (1) Settel, E.: Am. Pract. & Digest Treat. 8:443, 1957. (2) Johnson, H. J., Jr.: Am. Pract. & Digest Treat., in press. (3) Council on Pharmacy and Chemistry, A.M.A.: New and Nonofficial Remedies, Philadelphia, J. B. Lippincott Company, 1957, p. 508.

*U.S. Patent Pending

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more immediate tetracycline

Restricted sodium intake *not* a contraindication. Contains at most 7 mg. sodium per capsule.

SUPPLY	Tetracycline phosphate complex equiv. to tetracycline HCl (mg.)	Packaging
Capsules (per capsule)	250	Bottles of 16 and 100
Suspension (per 5 cc.)	125	2 oz. bottles
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Minimum adult dose: 250 mg. q.i.d.

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Minimum adult dose: 250 mg. of tetracycline q.i.d.

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GASTROINTESTINAL INFECTIONS

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BACTERIAL INFECTIONS COMPLICATING INFLUENZA

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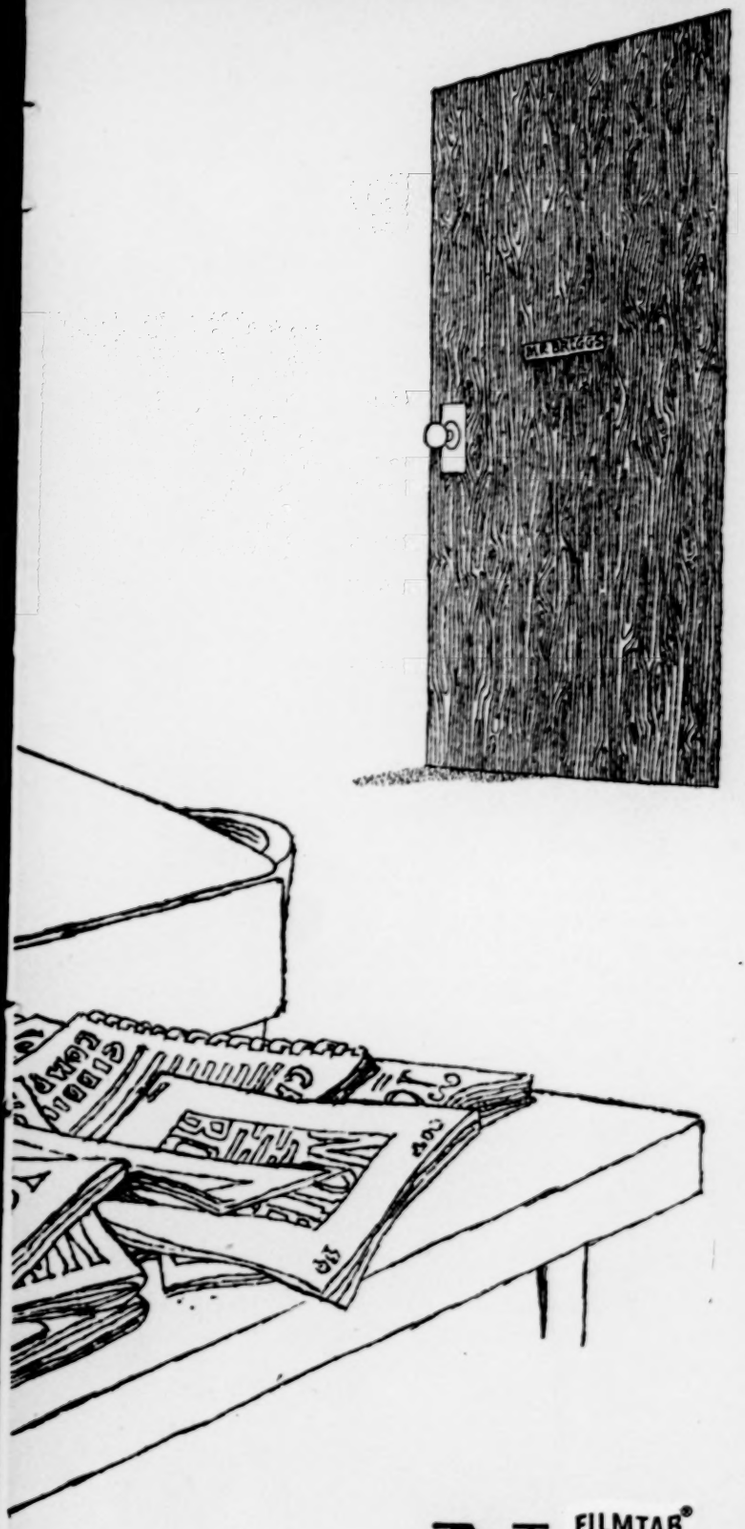
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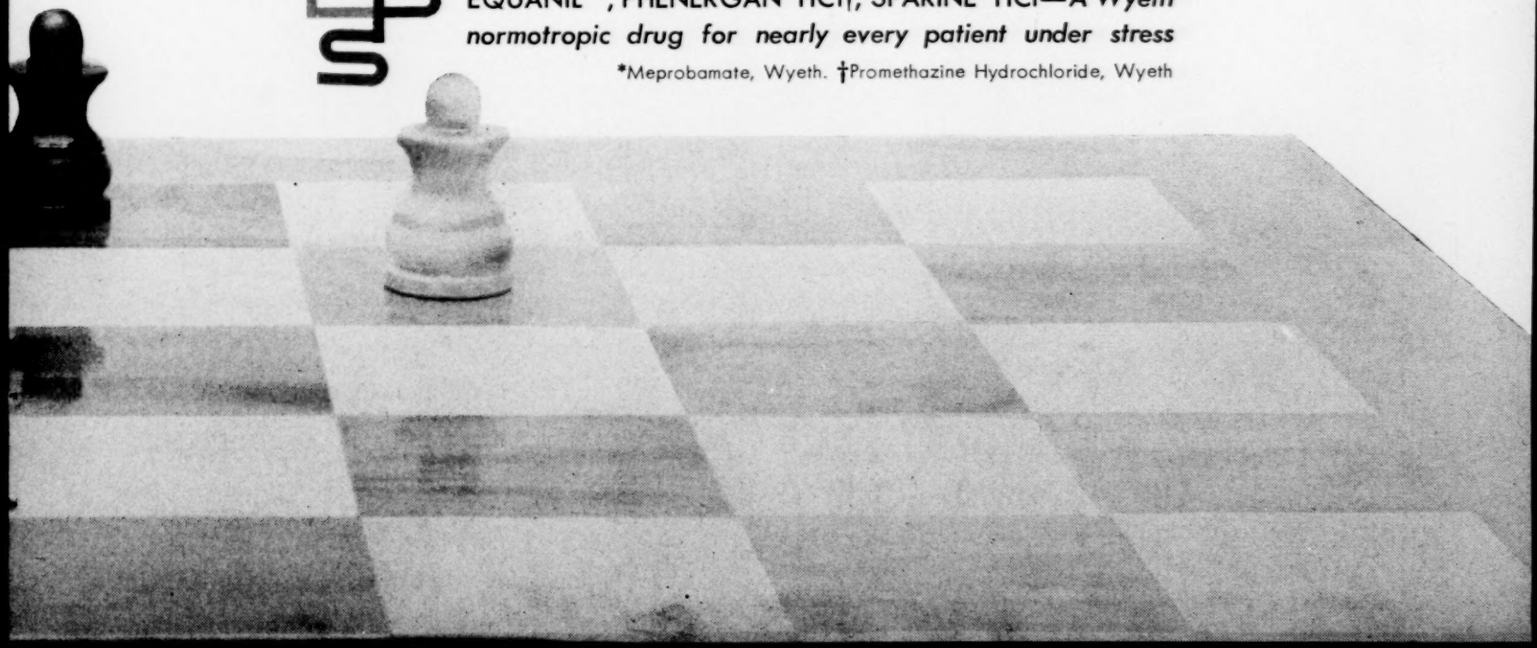
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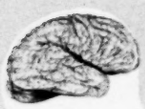
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†Cohen, B. M.; Cross, E. B., and Johnson, W.: Am. Pract. & Digest Treat. *6*:1030, 1955

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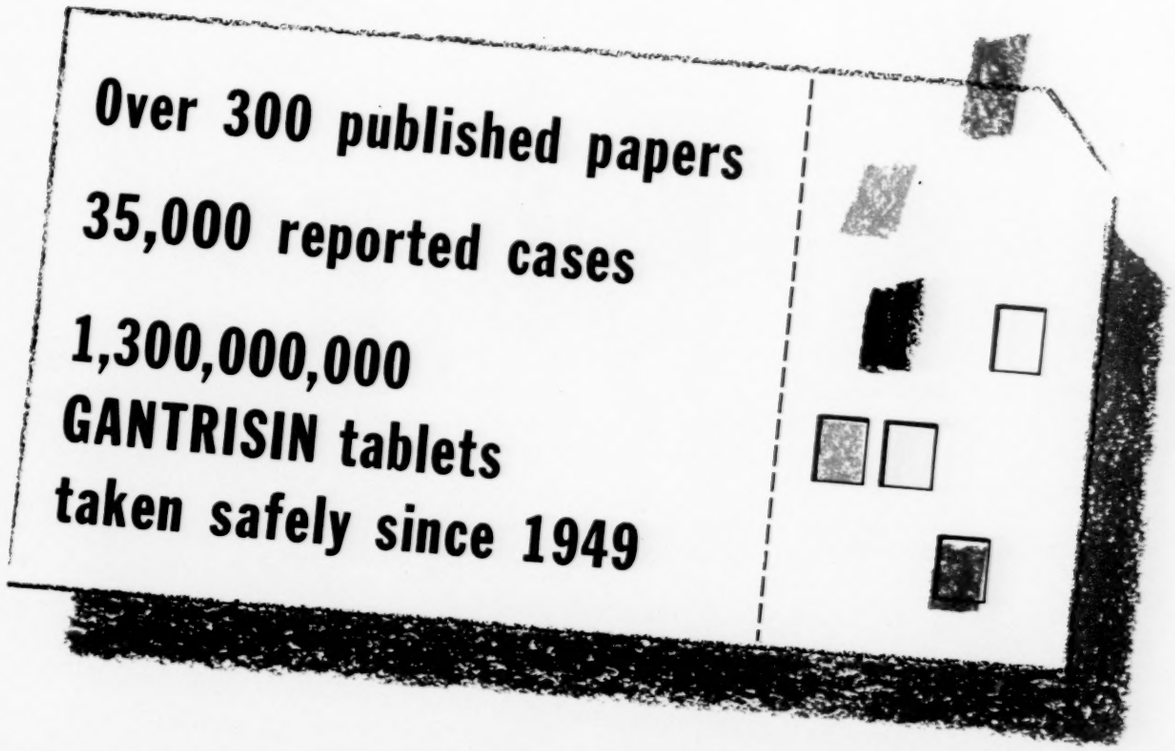
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Bibliography. Orgain, E. S.: Postgrad. Med. *17*:318, 1955. Finnerty, F. A.: Am. J. Med. *17*:629, 1954. McCall, N. L.; Sass, D. K.; Wagstaff, C., and Cutler, J.: Obst. and Gynec. *6*:297, 1955. Cohen, B. M.: New York State J. Med. *55*:653, 1955. La Barbera, J. F.: Med. Rec. and Annals *50*:242, 1956. Voskian, J.; Assali, N. S., and Noll, L.: Surg., Gynec. and Obst. *102*:37, 1956. Crisp, W. E., and McCall, M. L.: Am. Pract. and Digest Treat. *7*:620, 1956. Finnerty, F. A.: Am. J. M. Sc. *229*:379, 1955.


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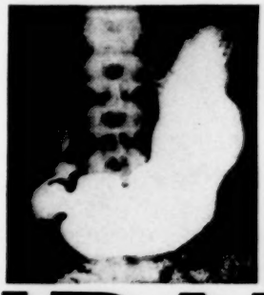
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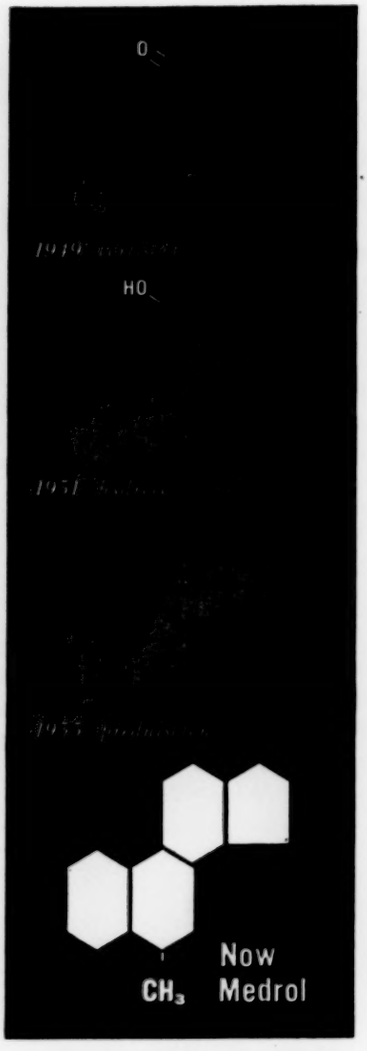
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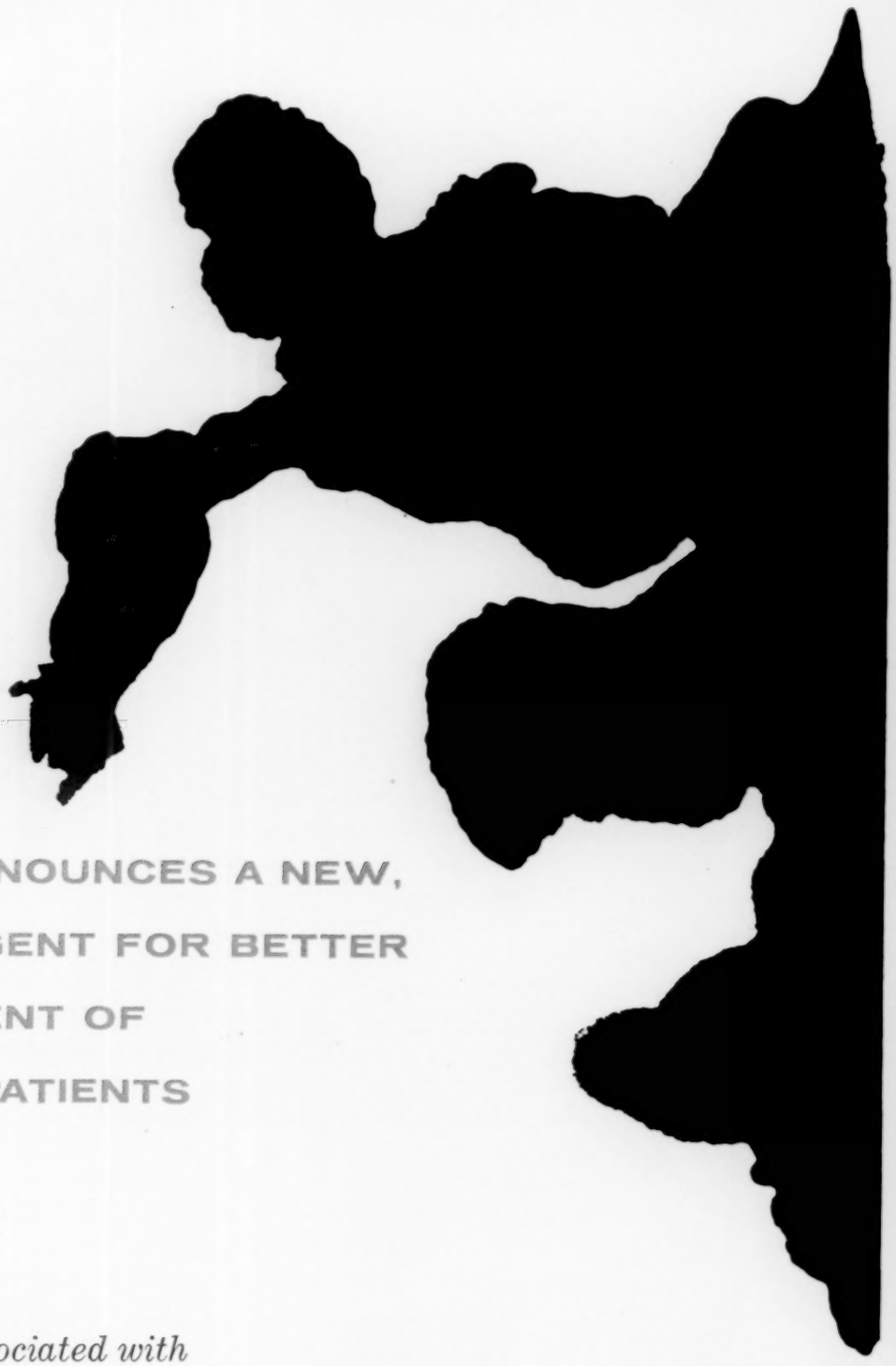
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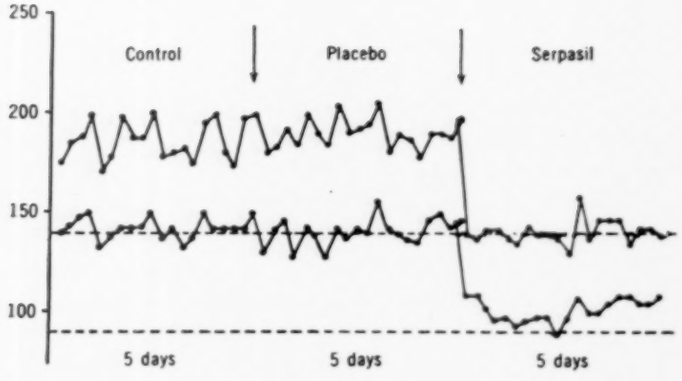
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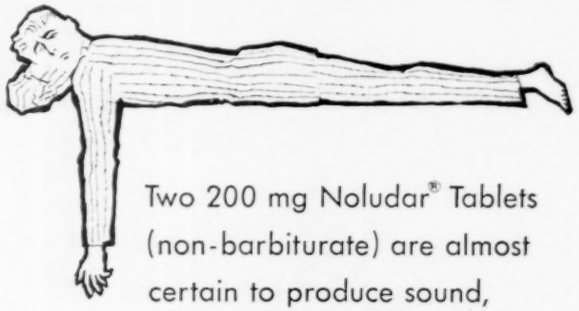
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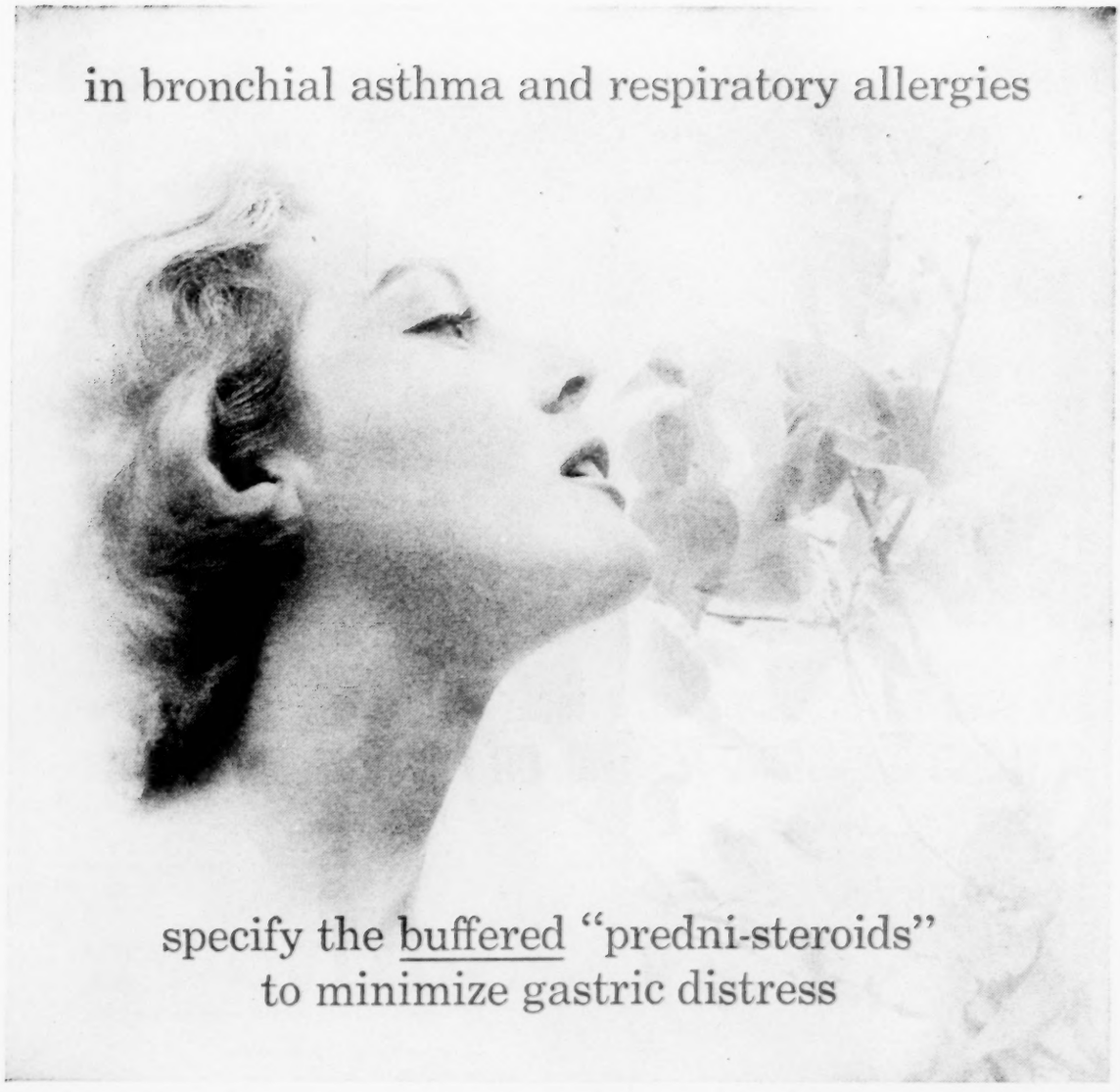
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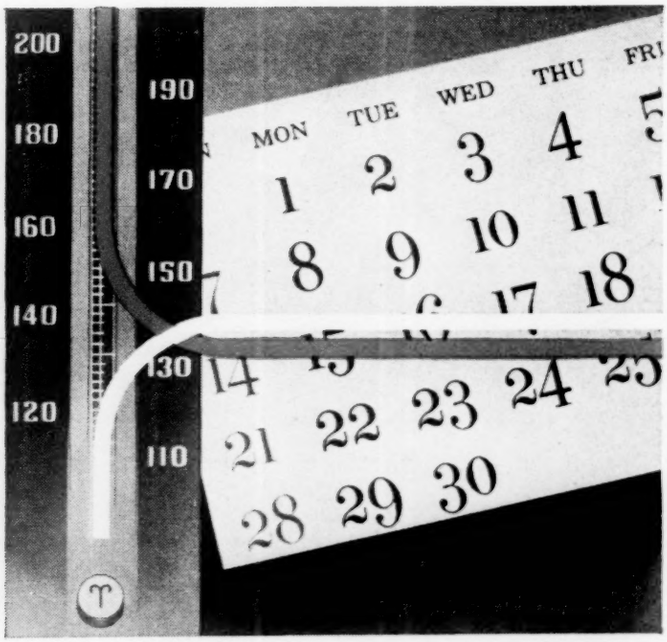
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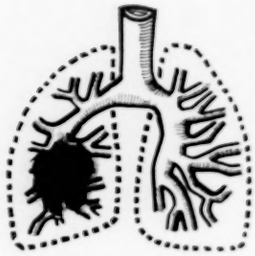
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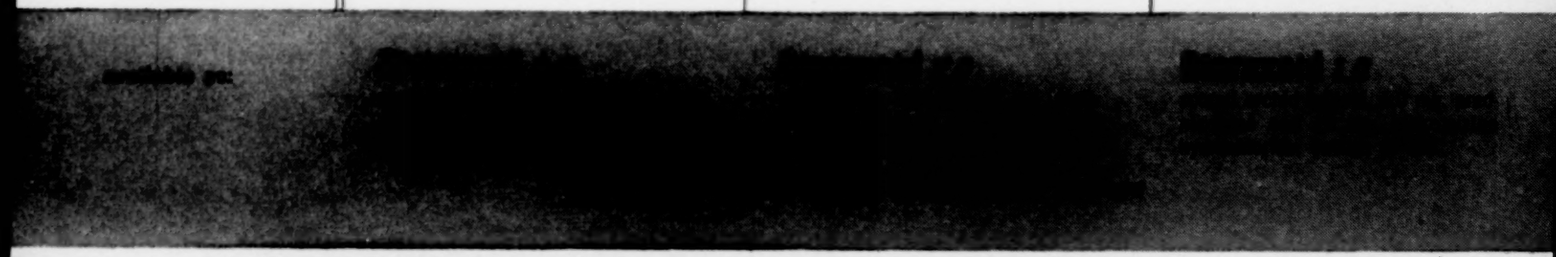
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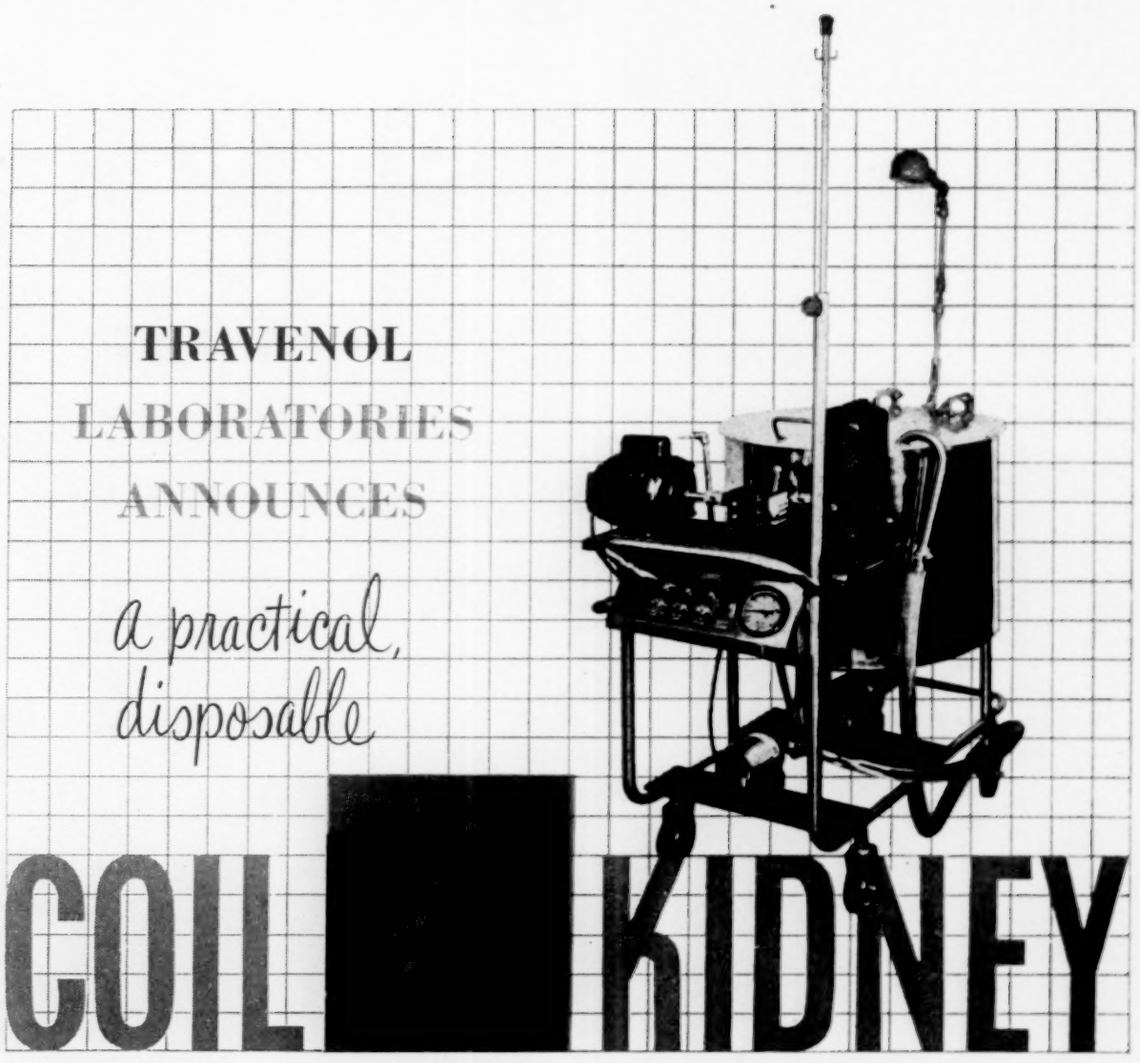
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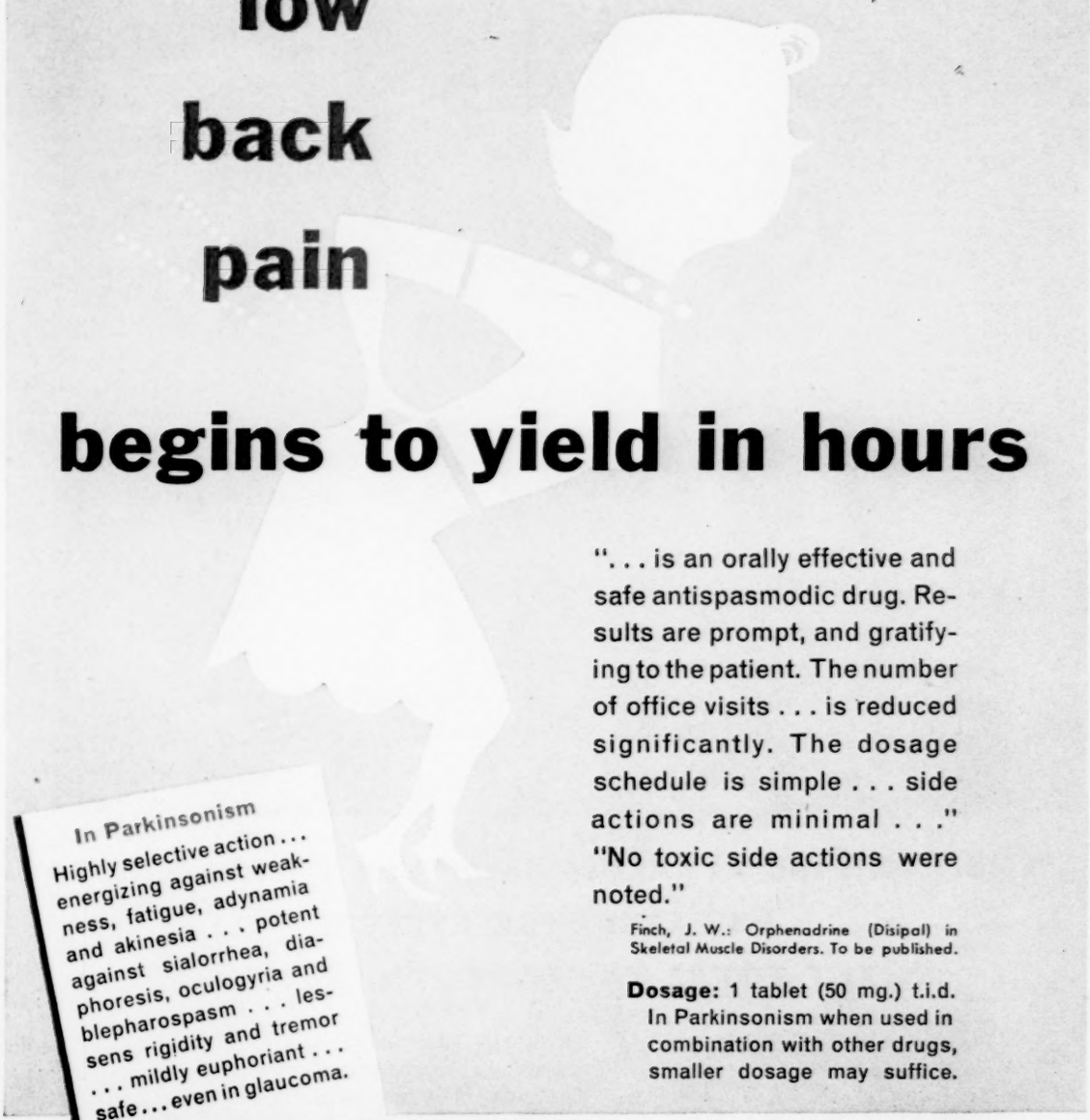
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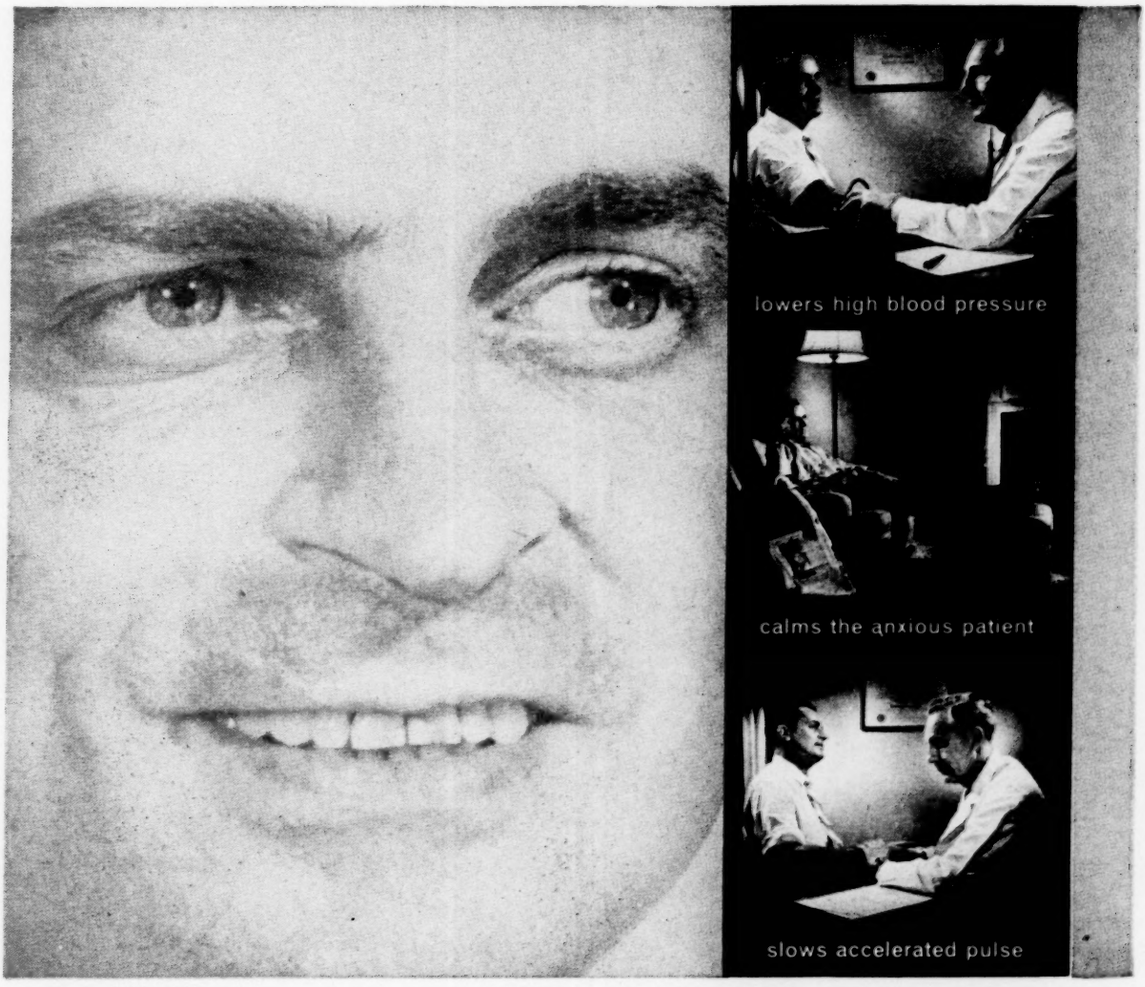
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1. Wright, W.T., Jr.; Pokorny, C., and Foster, T.L.: J. Kansas M. Soc. *57*: 410 (July) 1956.
2. Moyer, J.H.; Dennis, E., and Ford, R.: A.M.A. Arch. Int. Med. *96*: 530, 1955.

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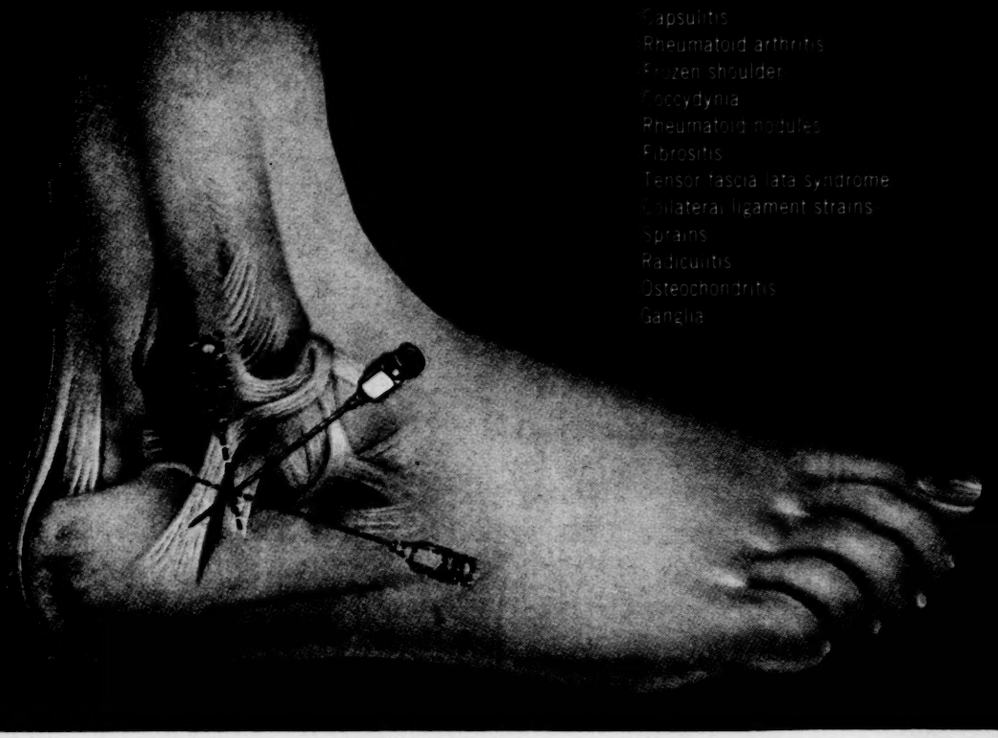
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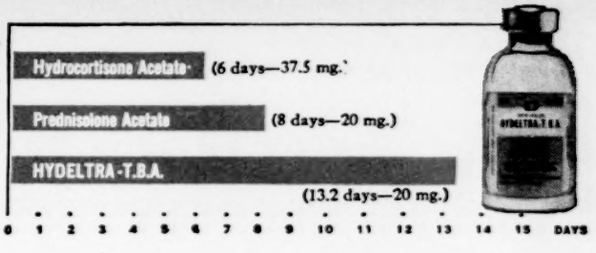
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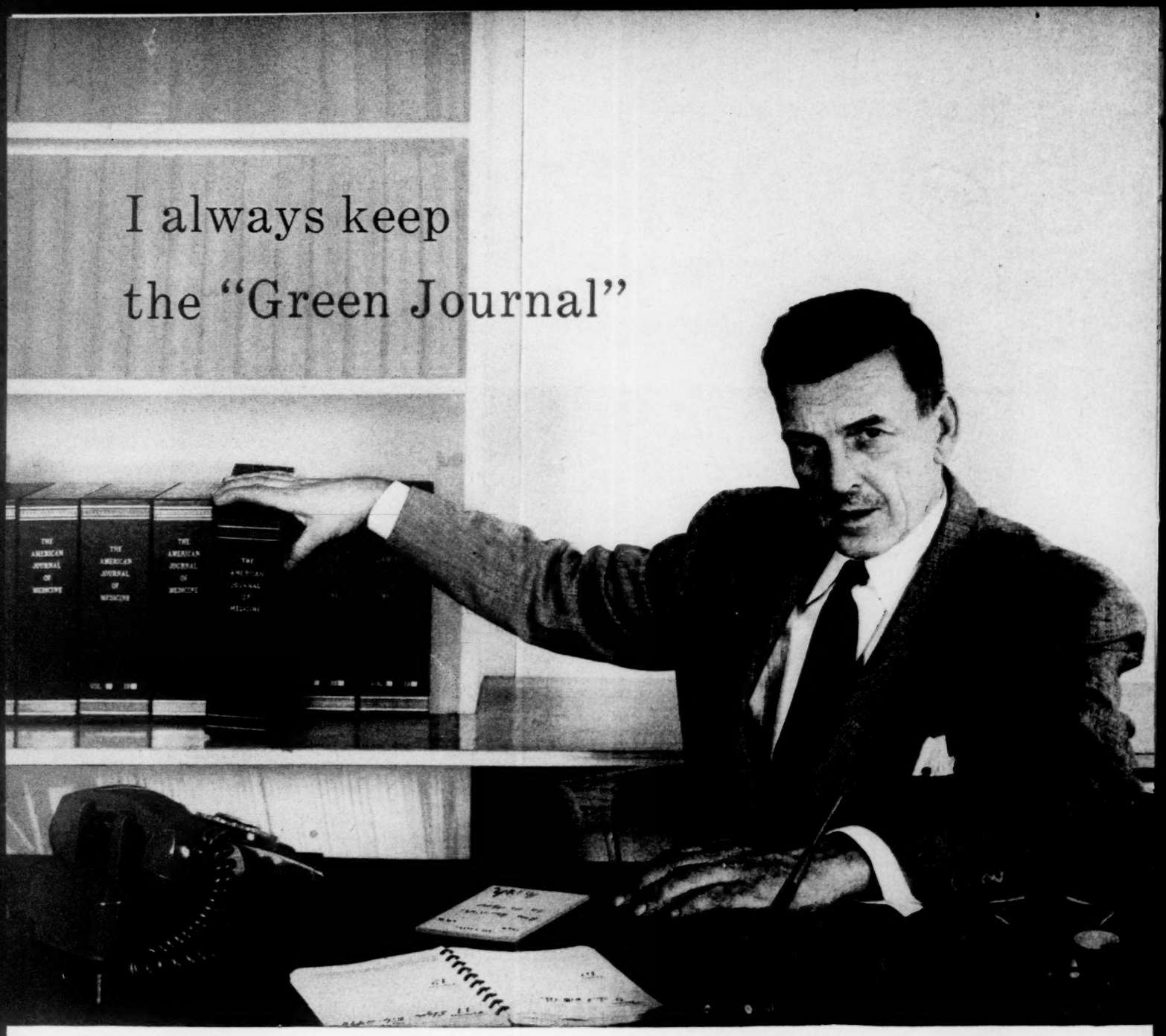


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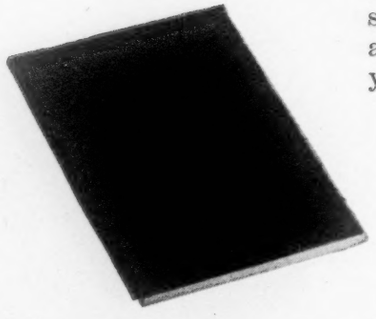


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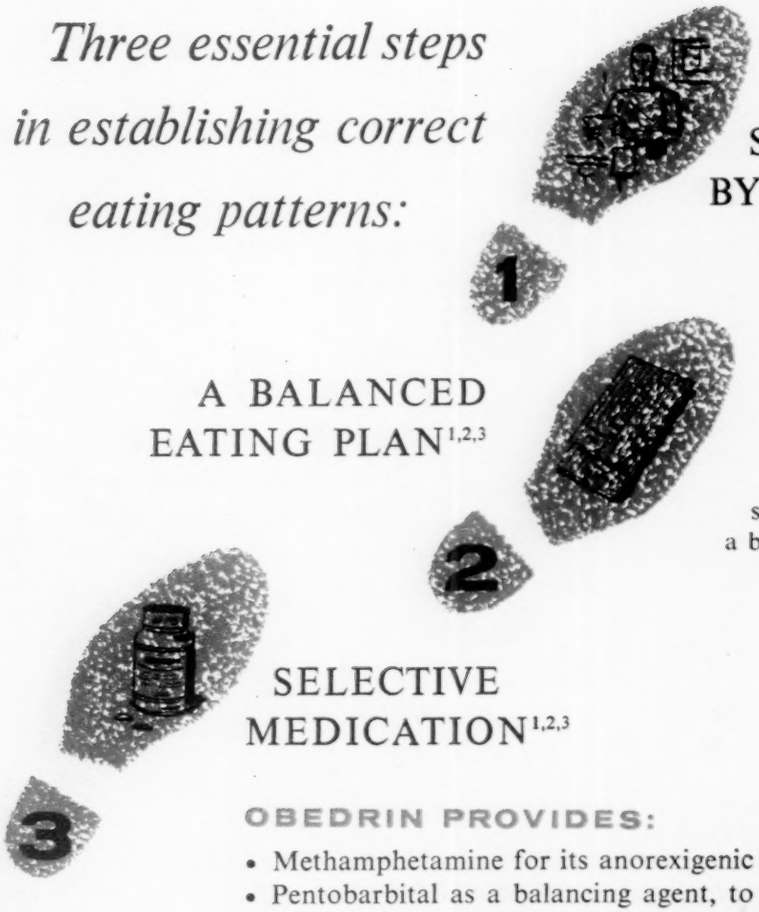
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1. Eisfelder, H.W.: Am. Pract. & Dig. Treat. *5*:778 (Oct. 1954).
2. Freed, S.C.: G.P. *7*:63 (1953).
3. Sherman, R.J.: Medical Times, *82*:107 (Feb. 1954).

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The American Journal of Medicine

VOL. XXIII NOVEMBER, 1957 No. 5

Foreword

THE peripheral vascular system has long afforded the investigator a fruitful area for conducting basic research. The clinician has also been able to describe a number of interesting phenomena, syndromes and diseases involving this system. Recently greater interest in the physiology and pathology of the blood vessels has been aroused by the rising incidence of diseases of the peripheral circulation in our aging population. Need for further research is accentuated by current evidence which suggests that vascular diseases are separable from aging *per se* and may be susceptible to preventive as well as therapeutic measures.

As in many fields of medicine, authoritative opinion on the vascular system seems at times to lack continuity or even to be contradictory. When such opinion is summarized by a single writer, he is inclined to present the material in a personal way that minimizes the discontinuities and contradictions, leaving the reader with the false impression that there is little left to be done. Therefore, *The American Journal of Medicine* has presented us with the unusual opportunity of inviting seven authorities in the field of peripheral vascular physiology and peripheral vascular diseases to review independently for one symposium some special aspects of these subjects. This characteristic of independent appraisal is emphasized by the presence of two physiologists, three physicians and two surgeons on the "panel" of the symposium.

Dr. Greenfield describes the results of recent investigations of the dynamics of the flow of blood through the peripheral vessels and the methods used to make these observations. His comments concerning the application of these methods should be helpful to anyone who wishes to evaluate their use. Also he discusses the very important recent advances in knowledge of the autonomic control of blood vessels of the extremities.

The important recent contributions to knowledge of the microcirculation have been carefully reviewed by Dr. Zweifach. His extensive experience in the use of the required special technics makes his evaluation of this information especially useful.

Knowledge of the tension of oxygen in a local area of the extremity may, under some circumstances, be of much greater interest than is the total blood flow in the extremity. Dr. Montgomery's article presents in a concise and interesting way information about tissue oxygen tension as it relates to the problems of peripheral vascular diseases. In addition, he discusses the methods required for obtaining these data.

The etiology of obstructive vascular disease is not so clear that an unquestioned best path for specific therapy is indicated. Thus, knowledge of numerous factors involved in producing the malady coupled with wide experience and cautious conclusions lead to the best available therapy. Dr. Wright has summarized his views of obstructive vascular disease and its treatment in just this way.

Diseases of the veins, like those of the arteries, emphasize the paradoxic situation of controversy concerning regimens of management, in spite of advanced knowledge of vascular physiology and of blood clotting mechanisms. Dr. Bauer summarizes his approach to diseases of the venous system on the basis of his extensive experience and investigation in this field.

The current medical management of patients suffering from obstruction of the peripheral blood vessels is presented from a different point of view by Drs. Hines and Gifford. Again it is apparent that experience usually governs the selection of therapeutic measures. Tests for

causative agents or for exact quantitation of obstructive disease do not as yet appear to play an important role in our approach to this group of diseases.

Recently surgery of the blood vessels themselves has resulted in dramatic improvement of blood flow to the involved extremities. Dr. Shumaker points out that this approach cannot be used on all patients with obstructive vascular disease and that care must be taken in selecting patients for these procedures. He also discusses the place of sympathectomy in the treatment of these conditions, particularly in relation to other modes of therapy. This article along with those of Drs. Hines and Gifford, and Dr. Wright, summarize current therapy in a way that should be of practical value to any clinician who treats patients with inadequate blood flow to an extremity.

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The Haemodynamics, Measurement and Nervous Control of the Limb Circulation*

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THE limb circulation must be assessed not only for its sufficiency at rest but, more importantly, for its ability to meet the demands of exercise in the muscles and of reparative hyperaemia in the skin. The rate of blood flow at rest may be normal in a limb in which arterial disease severely limits the hyperaemia of exercise [*47*] and following arrest of the circulation [*20*].

The circulation through a limb can be usefully thought of in terms of the relationship:

$$\text{Blood flow} = \frac{\text{Arteriovenous pressure difference}}{\text{Resistance to flow}}$$

or

$$\text{Resistance to flow} = \frac{\text{Arteriovenous pressure difference}}{\text{Blood flow}}$$

Blood flow is in ml. of blood per 100 ml. of limb per minute, arteriovenous pressure difference is in mm. Hg, and resistance to flow in arbitrary peripheral resistance units. Venous pressure fluctuates through so small a range that there can be no important doubt about the mean value. The mean arterial pressure may be estimated by applying planimetry to an accurate curve of intra-arterial pressure, by using a damped manometer or, more roughly, as one-third of the sum of the systolic pressure plus twice the diastolic pressure. Whether or not a steady pressure is haemodynamically equivalent to each of the family of fluctuating intra-arterial pressures of which it is the mean is at best doubtful. A comparison has never been made on the human limb, but the use of the mean pressure is a simple and probably a reasonable approximation to the truth.

The resistance to flow depends on the dimensions of the blood vessels and on the viscous properties of the blood. When a true fluid flows through tubes without turbulence, the viscosity is constant and independent both of the rate of flow and of the dimensions of the tubes; changes in resistance depend entirely on changes in the dimensions of the tubes. Blood, however, is not a true fluid, but a complex suspension, and it exhibits anomalous viscosity effects. The viscosity varies both with the rate of flow and with the dimensions of the tubes. Further, in atheromatous vessels there may be turbulence at the higher flow rates, and this increases resistance. Thus, although resistance depends mainly on the dimensions of the blood vessels, it depends to some extent on the rate of blood flow through them. Consequently, changes in vessel dimensions cannot always be inferred simply and with certainty from changes in resistance to flow. For example, a change of arteriovenous pressure difference with no change in vessel dimensions, may not only change the flow rate, but in addition, by changing the viscosity may change the resistance to flow.

The Circulation in Obstructive Arterial Disease. In the normal limb at rest there is only a slight pressure gradient along the main arteries and veins, for these offer slight resistance to flow. In Figure 1, the pressure at B is a little less than at A, and at C a little more than at D. The main resistance is presented by the small vessels, and the main drop in pressure is between

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B and C. During local muscular exercise, which we will suppose leaves the pressures at A and D unchanged, the resistance offered by the muscle vessels falls, and the flow through them increases. More blood flows along the main arteries and veins; the pressure falls at B and rises at C, but

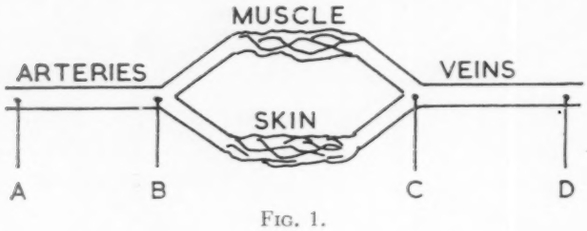


FIG. 1.

the main drop is still between B and C, and the pressure available for perfusing inactive tissues, such as skin, is only a little less than at rest. Thus the circulation through the muscle bed can be greatly increased without impairing that through the skin, and vice-versa.

In the limb with arterial obstruction, the resistance between A and B, offered by the main arteries and their collaterals, is often considerable, and of the same order as the resistance between B and C, offered by the vessels of the skin and muscle. Thus, even at rest, the pressure at B is much less than at A [*17*]. A normal rate of flow, however, is very often maintained by a compensatory fall in the muscle and skin resistance, and a comparatively small fall in resistance suffices for this compensation. During muscular activity, the resistance in the muscle bed falls, probably as much as in a normal limb, and the main drop in pressure is now between A and B. The resistance in the main arteries and collaterals is now the most important factor limiting the blood flow, and a very low pressure at B is available to perfuse the skin blood vessels.

Thus, in the normal limb, the low arterial resistance allows both skin and muscle circulations to draw on almost limitless amounts of high pressure arterial blood with only slight mutual interference. In the arteriosclerotic limb, the high arterial resistance places the skin and muscle circulations in competition for a limited amount of blood. Any measure which improves one circulation impairs the other.

In a limb with obstructive arterial disease, the more the resistance of the fine vessels is lowered, the more important becomes the effect of the obstruction in limiting the blood flow. Thus measures which cause a widespread dilatation of arterioles lower the resistance more in the normal areas than in the diseased areas, and in general divert blood to the former from the latter.

METHODS OF MEASUREMENT

This section deals mainly with methods that are easy to apply and which cause minimal discomfort. It is always important for the subject to be as comfortable, quiet and relaxed as possible. Draughts, direct sunlight and fluctuations in radiant heat and room temperature cause considerable disturbances in the limb circulation. An initial rest period of at least half an hour is desirable when critical measurements are to be made.

Venous Occlusion Plethysmography. The venous occlusion plethysmographic method still provides the most reliable quantitative measurement of limb blood flow. It is capable of following extremely rapid variations in flow, and, indeed, Burch [*8*] by a refined analysis of the records obtained from the finger tip, has been able to calculate the variations during a single cardiac cycle. Measurements can be simply repeated, and it is easily possible to measure flow six times a minute. Measurements can be made on individual digits, the hand or foot, the body of the hand, and the forearm or calf. Current practice is well described by Barcroft and Swan [*6*], and Greenfield [*24*] and Holling and Verel [*29*] give further detailed information about technic and interpretation.

Since the validity of the method is repeatedly questioned, the underlying principles are worth restating. Measurement is made of the rate of increase in limb volume during a brief arrest of the venous return. This is the rate of venous collection. Provided that the veins are completely occluded, the rate of venous collection is also the rate of arterial inflow during the observation. What is wanted, however, is the rate of inflow while the circulation is undisturbed by the venous occlusion. Provided that the method of occluding the veins does not directly interfere with the arterial inflow (as for example by the use of too high a pressure in the pneumatic cuff) it is assumed that the rate of arterial inflow is unaltered immediately after the onset of venous occlusion, and that the rate of venous collection immediately after occlusion equals the rate of inflow into the undisturbed limb before the occlusion. The chief support for this assumption is the observation that very often, especially in the forearm or the calf of the leg, the rate of venous collection continues unchanged for the

first ten seconds or more of venous occlusion. Thus if the arterial inflow changes at the onset of venous occlusion it must change instantaneously to a new and steady level. There is no sudden change in arterial pressure or venous pressure beyond the cuff [*25,50*] and it is difficult to imagine a mechanism which could instantaneously change the peripheral resistance to a new and steady level. An instantaneous change in the rate of inflow is therefore most unlikely. Moreover the rate of venous collection is usually found to be the same over a wide range of collecting pressures in the venous occluding cuff.

When the venous return is occluded, blood may not accumulate where it arrives. Therefore, it is desirable to enclose in the plethysmograph all the limb beyond the venous occluding cuff, or in the case of the forearm and calf, between the venous occluding cuff and a cuff arresting the circulation as completely as possible at the wrist or ankle. The method then measures the total rate of arterial inflow into this volume. It is possible, by careful iontophoresis of adrenalin® [*16*] to suppress the skin circulation, and the measurement then made is predominantly of the muscle flow [*14*]. Apart from this, the method does not directly distinguish between the rates of flow through the various tissues in the part.

The method is most satisfactory and certain when the limb is in a slightly raised position so that the veins empty by gravity between observations. It is easy to apply to the calf and forearm, for here the venous collection continues at a steady, and therefore easily measured, rate for a considerable time after inflation of the collecting cuff. It is less certain in the foot and hand, and particularly the digits, for here the rate of venous collection begins to decline very soon after the cuff is inflated, and there is difficulty and uncertainty in interpreting the records, particularly when the rate of blood flow is high.

The method needs special care, and the pressure in the collecting cuff must be suitably low, when there is unusually low pressure in the local arteries, as for example in obstructive arterial disease, during reactive hyperaemia [*35*] and other conditions causing a local vasodilatation, and when the limb is elevated [*29*]. During diastole, retrograde flow is to be expected at any point in the arterial tree where the downstream outflow relative to the downstream distensibility is less than the outflow rate relative to the distensibility in the remainder of the arterial tree. Retrograde flow occurs in the vasoconstricted [*50*] and in the elevated [*29*] forearm. Under these conditions, too high a pressure in the collecting cuff may cause it to act as a valve, preventing diastolic reflux, and artificially elevating the mean arterial pressure downstream. The method has been used by several observers [*7,21*] on dependent limbs. The veins are in this position already distended, and, although modest venous distention does not appreciably alter the apparent rate of inflow to the forearm [*25*] and to the calf [*12*], in the dependent position the serious lack of agreement between the results obtained by venous occlusion plethysmography and those obtained by other methods [*11,37,43*] throws doubt on the validity of the method.

In laboratory experiments, water filled plethysmographs [*23*] are preferred for their simplicity and reliability. The temperature of the water is easily controlled and adjusted, and the volume of the part under observation is well defined. Water temperatures of 30° to 32°C. for the hands and feet, and 34°C. for the forearm and calf are usually employed when it is desired to measure vascular reactivity. To permit movement, Shepherd [*46*] has devised a light celluloid plethysmograph which can be worn on the calf while walking, and can be used for measurements of flow immediately afterwards.

A device which imposes little restriction on the subject, and permits observations under a wide range of conditions, is Whitney's mercury-in-rubber strain gauge plethysmograph [*49*]. This consists of a thin and easily stretched rubber tube filled with mercury, which lightly encircles the forearm or calf. Changes in limb circumference cause changes in the electrical resistance of the mercury, and these are continuously recorded. Changes in volume are deduced from changes in circumference. Gauges at different levels on the forearm may simultaneously register rates of venous collection [*10*]. There is evidence that these different collection rates are due to different arterial inflow rates, rather than to redistribution of collected blood in the venous reservoir. This may not be so under all circumstances, but the possibility of distinguishing inflow rates to the muscular and tendinous parts of the forearm is useful. A very large number of such gauges regularly spaced along the forearm would theoretically supply the same information as the classic volume plethysmograph. In practice, Clarke and Hellon [*10*] found that a single strain-gauge plethysmograph about the middle of the forearm agreed quite well with the volume

plethysmograph. Unfortunately the method cannot be used for the hand or foot.

Another easily worn device for indirectly measuring changes in forearm or calf volume is the impedance plethysmograph [*32*], but it requires further testing before its reliability can be evaluated. For determination of flow, it would best be used in association with intermittent venous occlusion.

The Pulsation Volume. The fluctuations in limb volume during a single cardiac cycle are caused by phasic inequalities between the arrival and departure of the blood. Although in a steady position there may be fair agreement between the blood flow and the pulsation volume, no such relationship can be regularly assumed. For example, elevating the forearm may treble the pulsation volume while it reduces the volume flow [*29*], and in limbs with obstructive arterial disease the resting flow may be normal although the pulsation volume is extremely small [*47*]. The pulsation volume is initiated by the pressure fluctuations in the arteries, and these are much diminished distal to arterial obstruction, particularly when there is a collateral circulation. In the extreme case of a steady arterial pressure it is obvious that there would be no pulsation although blood flow might be entirely adequate.

Skin Temperature. This provides useful qualitative information about the circulation in the extremities of the limb. The influence of the local skin circulation on the temperature diminishes as one moves from the extremity to the root of the limb. In the proximal parts the temperature of the skin is much influenced by the temperature of the blood returning in superficial veins from more distal parts, and is somewhat influenced by the state of the circulation and metabolism in the deeper tissues. Observations are made on the uncovered skin in still air. If the circulation is arrested, the temperature falls to a level which, because of evaporation, is a little below that of the room air. If the circulation is maximal, in a healthy limb the temperature approaches that of the body core. Between these extremes, the relationship is complex and variable, but generally the temperature rises to within a few degrees of the maximum when the blood flow is only about one quarter of the maximum. Thus at the higher rates of flow, skin temperature is an insensitive and uncertain index of flow [*13*]. The temperature rises quite rapidly when the blood flow increases, but since the temperature falls very slowly even when the circulation is arrested, decreases in blood flow are poorly represented.

Surface Calorimetry. This is a semi-quantitative method which is easy to apply [*24*] and causes no discomfort to the subject, who simply immerses a part in stirred water. Blood flow can be deduced from the thermal measurements with fair confidence in the digits, and with less confidence in the hand or foot. Heat exchange is measured between an extremity and stirred water at a temperature some degrees different from, and usually 5°C. or more below, that of the body core. If in the equilibrium state the arrival and departure temperature of the blood were known, and if metabolic heat were neglected (it is very small by comparison with the heat conveyed by the circulating blood) the blood flow could be calculated by the Fick principle. Originally it was supposed that blood arrived at central body temperature and left at calorimeter temperature, and that all the available heat was therefore cleared from the blood to the calorimeter. In fact the blood arrives at a lower temperature than that of the body core, having already given up some of its heat on the way, and it leaves at a temperature above that of the calorimeter; thus only part of the available heat is cleared from the blood. Heat clearance is not 100 per cent, but some smaller and variable percentage, which in the case of the fingers may be about 90 per cent [*33*] and in the hand may be calculated from published data [*13*] to be about 75 per cent. Unfortunately, it is not possible in routine experiments to measure the arrival and departure temperatures of the blood. In fact, it is doubtful whether the mean departure temperature can be measured for the blood does not leave in a single vein, and to calculate the mean it would be necessary to know both the temperature and the flow in each of the several veins. Thus the blood flow cannot be rigorously calculated. It is, however, possible, by assuming 100 per cent heat clearance to arrive at a minimum figure for blood flow [*27*] which the actual flow certainly exceeds.

Precooling of arterial blood can be prevented by clothing the unimmersed part of the limb and heating it electrically so that the temperature of the skin is kept equal to that of the body core. Nothing can be done to improve the exchange of heat between the immersed part and the calorimeter.

The Adiabatic Calorimeter. The heat exchange

may be measured by immersing the extremity to a definite depth in well stirred water in an adiabatic calorimeter [*24,26,27,34*] the temperature of which is read each minute with a mercury in glass thermometer calibrated in hundredths of a degree centigrade. The water is normally arranged to be at about 29°c. at the start, and observations can usefully be continued until it reaches 32°c. If the volume of water in the calorimeter is suitably chosen in relation to the amount of extremity immersed, at least an hour of continuous observation is usually possible before the temperature reaches 32°c. If necessary, the water can then be replaced by an equal volume at 29°c., and after a few minutes observations can be resumed. The effect of the rise in water temperature in reducing the heat extractable from each volume of arterial blood is easily allowed for [*2,13*] but the physiologic effect on the blood vessels cannot be allowed for, and must be remembered. Fortunately, however, the latter rarely leads to difficulties in interpretation.

Heat Flow Discs. When an extremity is immersed in water, instead of measuring the total heat exchange between the tissues and the water the heat exchange between a sample area and the water can be conveniently measured by covering it with a copper-tellurium-copper heat flow disc [*28*]. These discs, 12 mm. in diameter and about 1 mm. thick, consist of an alloy of tellurium, coated on each face with fine copper gauze. The gauzes are connected by fine copper leads to a mirror galvanometer. When heat flows through the disc at right angles to its plane, it sets up a temperature difference between the faces, and so generates a thermoelectric potential. In an individual disc, the potential, and so the galvanometer deflection, is proportional to the rate of flow of heat. The discs are individually calibrated, since even discs of the same thickness exhibit small differences. A heat flow of 1 calorie per sq. cm. per minute may cause a temperature difference of about 0.9°c. between the faces, and generate a potential of 450 microvolts. The disc inevitably supplies some thermal insulation to the area it covers, but its thermal conductivity is such that this effect is small [*9*]. The effect is greatest at the finger tips, but even here, and at maximum vasodilatation, with discs of ordinary dimensions the temperature difference across the disc is a small fraction of the difference between the temperature of the arriving blood and that of the water.

It is important to secure good contact between the whole of one face of the disc and the skin, but pressures or tensions which may upset the local circulation are to be avoided. A useful adhesive is nobecutane made by Evans Medical Supplies, Ltd. The part is then covered with a thin and loose rubber glove or fingerstall, and immersed in stirred water at a suitable steady temperature, usually about 30°c. The sole purpose of this water is to maintain the outer face of the disc at a steady temperature different from that of the blood. Ideally, only the disc and the immediately adjacent skin should be immersed, since for maximum sensitivity arterial blood should arrive without precooling at the site of observation.

The heat flow disc behaves like a very small adiabatic calorimeter, and if it were possible to cover the immersed area entirely with discs, the total heat elimination, as measured by the calorimeter, could be measured. The advantages of the disc over the calorimeter are that it is easier to read the large deflections of the galvanometer than the small rises in temperature of the thermometer, that readings can usefully be made at intervals shorter than a minute, that the part can be immersed in water at a constant instead of a slowly rising temperature, that observations can be continued indefinitely, and that the precise depth of immersion is unimportant so that the subject has a certain limited freedom of movement. On the other hand, the disc by insulation and, on convex surfaces, by tissue pressure and distortion, is always liable to cause some local disturbance of heat flow, whereas the adiabatic calorimeter causes none.

Use and Interpretation. Surface calorimetry can be usefully employed under conditions of raised venous pressure [*42,45*] or lowered arterial pressure [*38*] which make venous occlusion plethysmography difficult and uncertain. The speed of response is limited by the thermal capacity and conductivity of the tissues between the blood and the surface, and the method is incapable of following accurately the most rapid changes in blood flow. For example, if the blood flow to the finger is suddenly arrested, the heat elimination does not immediately cease, but in successive minutes falls to about 60, 24, 12, 5 and 3 per cent of the value before arrest. The heat eliminated after arrest of the circulation comes from the tissues, which before arrest are at an average temperature above that of the water in the calorimeter. On release of the circulation,

the tissues are re-warmed by the blood, and at first only a portion of the heat brought by the blood is eliminated to the calorimeter. Consequently, during the period of reactive hyperaemia, when the blood flow is very high, the heat elimination may not rise above the resting level. Only when the blood flow has been steady for some time does the rate of heat elimination accurately reflect the flow. When the rate of flow fluctuates, the rate of heat elimination gives a delayed and smoothed picture of the rate of flow. It is, of course, important and not difficult to use apparatus with a fast response [*26*]; for example the recorded temperature of the adiabatic calorimeter should settle within one minute of adding a little hot or cold water.

Other Methods for Measuring Blood Flow. The following methods are each of value for special purposes, but unlike those already mentioned, they require the use of needles or catheters.

Under conditions in which tissue oxygen consumption may be assumed to be constant, changes in blood flow can be deduced from changes in the oxygen saturation of venous blood. In some persons catheters can be placed to collect venous blood from the forearm which appears to be derived exclusively either from skin or from muscle [*39*]. This permits the skin and muscle circulations to be studied separately.

Useful information about the human muscle circulation has been obtained [*3*] with the Hensel needle, which is essentially an internal calorimeter. The device is somewhat bulky in its present form.

The dye dilution method [*1*] would be simple to apply and interpret if there were a mixing device (corresponding to the heart) near the site of injection into the artery, or if the blood and dye all returned and became mixed in a single vein. Unfortunately there is neither a mixer nor a unique vein.

The rate of clearance of radiosodium from an injection site [*31*] depends largely on local blood flow, but was introduced by Kety as a measure of something even more important, the efficiency of the local circulation in its broadest sense. It can be used in sites difficult to reach by other methods. The length of useful observation after a single injection is somewhat limited, and repeated injections are not always justifiable. There is no time lag in the response, but the resolution of the method does not permit rapid fluctuations, such as in reactive hyperaemia, to be followed accurately.

THE NERVOUS CONTROL OF THE BLOOD VESSELS OF SKIN AND MUSCLE

This subject was treated in a monograph of Barcroft and Swan in 1953 [*6*]. The present section is mainly concerned with advances in knowledge since that time. Most of the observations have been made on the upper limb, and it is not yet known whether similar conclusions apply to the lower limb, although it is very probable that they do so.

The Hand. The most important control is exercised by the sympathetic vasoconstrictor fibres, which are capable, when active, of reducing the blood flow to about one fortieth of that which is seen when they are blocked.

Sympathetic vasodilator fibres, if present, play a very minor role. During body heating, blocking the vasomotor nerves does not reduce the blood flow [*2,19,43*]. Thus although Lewis and Pickering [*30*] obtained evidence in cases of Raynaud's disease for the existence of vasodilator nerves to the skin of the hand, these have not been shown to play a measurable part in the control of the circulation in the normal hand.

The Skin of the Forearm. Both vasodilator and vasoconstrictor nerves regulate the circulation through the skin of the forearm. Of these, the vasodilator nerves, first described by Grant and Holling [*22*], are the more important. The role of the two sets of nerves is displayed by following the changes in total forearm blood flow on warming a rather cold subject. These changes are now known to be due entirely to alterations in the blood flow through the skin [*16,39*]. Roddie, Shepherd and Whelan [*40*] distinguish two steps. The first step is an increase in flow from about 2 ml. to around 4 ml./100 ml./minute. This increase is of the same order as that which follows blocking of the cutaneous nerves [*4*] and may be presumed to be due to withdrawal of vasoconstrictor activity. The subject is now comfortable. The second step, seen on further heating the subject, and accompanied by the onset of sweating on the arm, is an increase in flow from around 4 to about 10 to 15 ml./100 ml./minute. The blood flow [*15,40*] and the oxygen content of the blood in superficial veins draining the skin [*41*] now far exceed that following block of the cutaneous nerves, and, further, the second step can be delayed although not prevented by doses of atropine which block the action of intra-arterial acetylcholine. Thus the second and

larger step depends on nerves which actively cause vasodilatation, and at least partly do so by a cholinergic mechanism. Recent observations [*18*] suggest that the vasodilatation is brought about by bradykinin production resulting from sweat gland activity, so that the question whether the nerves cause vasodilatation directly or indirectly is not settled.

The Muscles of the Forearm. Compared with the changes in blood flow brought about by exercise, the changes brought about by variations in the nervous control of the muscle vessels are very modest. Exercise can raise the total forearm flow from a resting value of about 3 ml. to about 30 ml./100 ml./minute. Blocking the deep nerves to the forearm [*4*] increases the blood flow only to about 7 ml./100 ml./minute, and some part of this increase is in the blood vessels of the skin. Nevertheless, there is convincing evidence [*4,37,41*] for the existence of vasoconstrictor nerves, and under ordinary conditions of rest these maintain a tonic contraction of the muscle vessels.

This vasoconstrictor tone is not released by body heating, for this has now been shown by four independent methods not to affect the muscle blood flow. During general body heating Barcroft et al. [*3*] detected no increase in muscle flow by the Hensel needle; Edholm et al. [*16*] were able by iontophoresis of adrenaline into the skin of the forearm to prevent any increase in forearm blood flow; Roddie et al. [*39*] observed a large increase in the oxygen content of the blood in superficial veins draining the skin, but not in deep veins draining the muscles; and McGirr [*31*] detected no change in the clearance rate of radiosodium from the muscles.

The vasoconstrictor tone, however, has been shown by Roddie, Shepherd and Whelan to be released by stimulation of baroreceptors in the low pressure side of the circulation. Passively raising the legs of a recumbent subject persistently increased the forearm blood flow by as much as 5 ml./100 ml./minute. The increase was much reduced if blood was trapped in the legs by a cuff on the thighs at 80 mm. Hg, but the increase promptly followed release of the cuff. The increase in flow was confined to the muscles, for there was an increase in the oxygen saturation of the blood in the deep veins draining them but no change in that of the blood in the superficial veins draining the skin. The vasodilatation is mediated through the sympathetic nerves, for it is abolished by sympathectomy. It can be accounted for by a reduction in the activity of vasoconstrictor nerves, for the blood flow is raised to about the level achieved by block of the deep nerves in the opposite arm [*37*]. Further, when the subject is tilted into the head down position, the oxygen saturation of the deep venous blood increases towards, but does not exceed, that in the opposite arm with the nerves blocked, and administration of atropine does not alter the response [*36*]. The normal conditions of life under which the vasoconstrictor tone to the muscle blood vessels is released have yet to be defined.

Vasodilator nerves to the muscle blood vessels of animals have been clearly demonstrated [*48*] and they can be made to discharge by electrical stimulation of parts of the brain. The physiologic stimulus provoking their discharge has not yet been elucidated. In the human being the evidence for vasodilator nerves to muscular blood vessels rests on observations during fainting; blood flow was for a short period greater in the intact forearm (average, 5.3 ml./100 ml./minute) than in the nerve blocked forearm (average, 3.3 ml.) [*5*]. Assuming that the blood flow through the skin of the forearm is reduced, like that through the hand, the greater blood flow on the unblocked side must be through the muscle and must be brought about by vasodilator nerves. The evidence is not quite conclusive, because vasodilatation in the skin of the forearm, although unlikely has not been directly excluded, and secondly the blood flows in the blocked and unblocked forearms were not observed simultaneously. Further observations are required to confirm the existence and to elucidate the range of action and the normal stimulus for activation of vasodilator fibres to human muscle blood vessels.

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General Principles Governing the Behavior of the Microcirculation*

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The successful achievement of tissue homeostasis is dependent upon regulatory mechanisms which are unique to the terminal vascular bed, and function independently of the remainder of the circulatory system. In general, the reactions of the peripheral blood vessels fall into three main categories: the maintenance of blood pressure (arteries and arterioles); the local regulation of blood flow within the tissue proper (terminal arterioles, precapillary sphincters and capillaries); and the return of the blood to the heart (the muscular venules and veins). In the general area of blood pressure regulation, two attributes of the larger arteries and arterioles are of importance. The general compliance or distensibility of the vessels, an intrinsic physical property governed in the main by its elastic tissue elements [1]; and active changes in caliber mediated by the contractile smooth muscle elements [2].

There are a number of important differences in the basic properties of the smaller blood vessels as conduits in comparison with larger vessels. The distensibility of the muscular arterioles is a function of the prominent smooth muscle component. As a consequence, the tension-length relationship in the small vessels does not follow purely physical laws, since the muscle tone, unlike the elastic tissue factor in large blood vessels, represents a variable and an actively modulated property [3]. The loss of its connective tissue investment removes the small blood vessels from the status of a separate compartment and makes the vessel wall an integral part of the tissue. This contingency exposes the smooth muscle and endothelial elements to the environmental influence of the tissue metabolic milieu and introduces a new set of regulatory mechanisms. A waning in the regulatory influence of the sympathetic nervous system becomes apparent concurrent with the structural alterations [3]. Not only are the vessels in the terminal vascular bed under the predominant influence of humoral factors but, as a consequence of their extreme sensitivity to vasoactive agents, show a considerable latitude of independence of the remainder of the circulatory system [5].

One other feature distinguishes the microcirculation. The local introduction of vasoactive principles gives to this agency the ultimate control of the tissue circulation, to the extent that local factors can override systemic stimuli, even when they are of maximal intensity. The sympathetic nervous system, thus, serves to modulate the changes in peripheral circulation, integrating them with the activity of the larger blood vessels.

STRUCTURAL CONSIDERATIONS

Perhaps the outstanding characteristic of the capillary circulation revealed by direct microscopy is the continuous state of flux of the blood flow. Changes can be seen in the rate, direction of movement and total volume of flow, as well as in the number of capillaries with an active circulation. During the ebb and tide of flow an efficient circulation persists in certain channels, whereas the majority of the capillaries show an intermittently active circulation. In most tissues the same, centrally located vessels serve as thoroughfare or preferential channels [6]. These vessels are the direct continuations of the feeding arterioles and, like the parent structures, are invested with smooth muscle. In the more distal ramifications, the muscular coat becomes discontinuous and difficult to recognize. It is only through the combined use of histologic criteria and the functional response to vasoactive agents that the distribution of smooth muscle has been clearly established [7]. The distinctive arrange-

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ment of muscle at the bifurcation of the numerous side branches and their function as vascular sphincters was recognized by many investigators [*8,9*]. Because of their strategic location, the vasomotor activity of the precapillary sphincters is responsible for the alternating flow through the capillaries, since the latter vessels are essentially endothelial tubes with no contractile properties. The true capillaries have numerous, randomly placed cellular elements adherent to the vessel wall. At one time, investigators were of the opinion that many of the so-called pericytes were modified muscle cells and were responsible for the active vasomotor changes exhibited by the microcirculation [*10,11*]. Current opinion [*12–14*] holds that only occasional vessels of the metarteriolar type possess branched smooth muscle cells as described by Rouget [*15*], Vimtrup [*16*], Krogh [*10*] and others.

In the older literature, the bed was depicted as arising from the repeated subdivisions of the terminal arteries, the haphazard interanastomosis of these channels and their joining up with one another to form the venous system. Actually, the majority of the capillaries do not lie in the direct path of blood flow from arterioles to venules. This arrangement permits the removal of most of the capillaries from the active circulation at certain periods without hindering the flow through the more centrally routed preferential channels.

The architectural pattern of the capillary bed is, thus, peculiarly suited to cope with variations in the amount of blood it must distribute [*17*]. Although some details of the bed may differ, its basic elements appear to be fundamentally the same in all tissues. The primary structural units are the direct extensions of the arterial tree, the metarterioles, which serve as the framework for the distribution of capillary vessels. The metarteriole is discontinuously surrounded by smooth muscle cells which are most numerous in the proximal and absent in the distal portion of the vessel. At the proximal end of the metarteriole, precapillary vessels emerge at acute angles. Each precapillary is surrounded for a short distance by a continuation of the smooth muscle of the parent stem, an arrangement which permits these structures to act in effect as a sphincter and has given rise to the term "precapillary sphincter." The precapillary vessels in turn subdivide to form the network of true capillaries.

The venous side of the system originates in several ways. In most tissues the direct extensions of the metarterioles merge imperceptibly into vessels which receive incoming capillary blood and serve as the major tributaries of the venous system. In other areas several capillary networks fuse with one another to form large postcapillaries which gradually assume the structural characteristics of the venules. In still other situations direct shunts divert blood back into the venous system and serve as focal points for the drainage of capillaries into the effluent circulation.

Another structural feature of the capillary bed which deserves emphasis is the fact that coincident with the extensive branching of the terminal arteries and arterioles, these vessels interdigitate to form a series of arcuate structures from which the branches to the capillary bed proper are distributed [*18,19*]. This arrangement presumably serves to provide a uniform pressure throughout the bed and ensures a more adequate collateral circulation. The arcuate pattern is seen most frequently in flat, extensive structures such as the omentum, the undersurface of the skin, the interfascicular connective tissue, and on the surface of hollow viscera, such as the intestinal tract and urinary bladder. Arcuate interconnections are also seen between the muscular venules, with the central portion of the linking vessel exhibiting a reversal of flow as the pressure conditions change.

INNERVATION

The evidence pertaining to the sympathetic innervation of the terminal vascular bed is both sketchy and controversial. Histologic studies [*20*] which *perforce* deal with small segments of the peripheral vascular tree are difficult to evaluate because of technical shortcomings, incompleteness of the staining and the inability to obtain an over-all picture of the neurovascular relationship. Many of the physiologic studies [*21*] on the other hand, had no means of determining which of the vascular units were involved. Perhaps the outstanding impression derived from the literature is the incomplete and at times indiscriminate distribution of nerves to the smooth muscle elements beyond the arterioles. The existence of what appears to be a fine reticulum of nerves about the true capillaries [*22*] is open to question. In fact, aside from a fortuitous juxtaposition, there is no clear-cut evidence of an innervation of non-muscular endothelial vessels [*23*].

As in the case of the larger vessels, there is a

considerable body of histologic and physiologic evidence to indicate that the muscle cells of the terminal arterioles are under the control of the nervous system [*24*]. Sympathetic nerve fibers can be seen to ramify in direct contiguity with the smooth muscle elements. When the arteriolar muscle coat becomes thinned and discontinuous, the muscle cells are less regularly supplied by nerves. The precapillary sphincters show a seemingly haphazard distribution of nerve connections, as determined by histologic and physiologic studies. Denervation experiments suggest some form of sympathetic innervation of the capillary bed, since both surgical and pharmacologic sympathectomy lead to an increased reactivity of the muscular vessels [*25*]. The possibility should also be considered that nervous stimulation might release humoral material proximal to the bed, which would then be carried by the bloodstream and act more peripherally. However, in view of the rapid destruction of such vasoactive materials, this contingency is probably not of major importance under normal conditions. Lutz and Fulton [*26*] described a dilation of the smaller muscular vessels following nerve stimulation and believed that their evidence supported the existence of both vasoconstrictor and dilator nerve fibers. The possibility should be considered that purely constrictor fibers are concerned in both instances, and that stimulation of a peripheral nerve fiber may lead to a diminished vasoconstrictor tone, rather than a direct vasodilator action.

Further evidence for the importance of the nervous system in the activities of the microcirculation was obtained in experiments in which vascular reactivity was studied following sympathectomy. As is well known, denervation results in a heightened responsiveness of vascular smooth muscle to constrictor agents such as epinephrine or norepinephrine [*27*]. The development of hyperreactivity in the capillary bed proper following dorsolumbar sympathectomy is manifest by a shift in the threshold concentration of epinephrine required to elicit a constrictor response in the metarterioles and precapillaries [*28*]. Immediately following sympathectomy, during the first ten to fifteen days, vascular reactivity increased about fifty-fold. Thereafter the response to epinephrine returned gradually to more normal levels until at about sixty days after surgery, vascular reactivity was normal. On the other hand, the fact that overactivity of the sympathetic nervous system or stimulation of sympathetic fibers directly leads only to a contraction of metarterioles and precapillaries in scattered portions of the system would indicate a somewhat loose anatomic relationship between the sympathetic system and the smooth muscle elements in the capillary bed proper.

Thoracolumbar sympathectomy in the dog has no discernible effect on the caliber of the metarterioles and precapillaries in the omentum observed from two to sixty days after surgery [*28*]. Ganglionic blockers (hexamethonium chloride and arfonad®) produced dilation of the feeding arterioles but not of the metarterioles or precapillary sphincters [*25*]. Even epidural spinal anesthesia (procaine) did not significantly alter the pattern of blood flow within the mesenteric bed. As indicated in another section, most procedures which affect the peripheral sympathetic system interfere with the pattern of spontaneous vasomotion but do not abolish this activity. Since in the case of spontaneous vasomotor movements we are dealing with an overlapping of neurogenic and humoral mechanisms, any effect on either of the two regulatory processes may be reflected by changes in the other.

CAPILLARY CONTRACTILITY

There is almost universal agreement today that activity changes in caliber within the capillary bed proper are initiated by smooth muscle [*29*]. Inasmuch as the distribution of smooth muscle is not uniform, the capacity to regulate the local blood flow is dependent upon the number and arrangement of the muscular vessels. In the capillary systems of skeletal muscle, the surface of the bowel and sheaths of connective tissue the large majority of the vessels are nonmuscular endothelial tubes. In other areas, such as the skin, urinary bladder and conjunctival surface of the eye, most of the vessels in the capillary bed are muscular.

Some authors have described phenomena which they have attributed to endothelial contraction. Thus, Sanders et al. [*30*] found that stimulation of the cervical sympathetic elicited in the ear of the rabbit a narrowing of certain capillary structures, apparently due to an active contraction of the endothelium proper. Such a change, however, was not uniform and may have been induced by perivascular muscle cells which are extraordinarily difficult to recognize in the living state. When the metarterioles of different

mammals are examined under high magnification in transparent structures such as the mesentery, it can be seen that the endothelial cells show an almost continuous movement, which some authors have described as resembling ameboid movement [*31*]. It is difficult to ascertain whether these changes are due to the activity of the smooth muscle or to that of the endothelial cells themselves. Factors which reduce the tone of smooth muscle lead to a disappearance of this type of endothelial movement. The endothelium of true capillaries does not exhibit a similar pattern of activity when examined carefully. Lutz and Fulton [*26*] describe a narrowing only of the arteriolar or precapillary portion of the vessel following stimulation of the sympathetic nerve fibers with microelectrodes in the hamster cheek pouch.

Endothelial Tone. The true capillaries do not exhibit what might be interpreted as active changes in caliber [*32*]. In the case of the muscular components of the capillary bed, constrictor stimuli (chemical, mechanical, electrical) bring about a rapid reaction sufficiently pronounced to diminish or halt the blood flow. On the other hand, the caliber of the true capillaries remains remarkably constant despite extreme fluctuations in flow and is unaffected by physiologic stimuli. Endothelial cells, in common with other living cells, exhibit a state of normal tone, which is essentially a reflection of the state of health, so to speak, of the cell. The tone of cells in general is reflected for the most part by changes in water content. We can only speculate on the extent to which impairment of cell tone is due to changes in the cell surface, the avidity of the cytoplasmic constituents for water, electrolyte shifts or metabolic factors. When damaged by an agent such as histamine the endothelial cell becomes swollen in appearance and loses its normal elastic properties.

The caliber of the capillaries is usually just sufficient to permit a single column of red cells to pass through. It is only in structures such as skeletal muscle, in which a considerable tissue pressure can be exerted on the capillary vessels, that situations are encountered in which the capillaries are narrower than the red blood cells [*10*]. In most tissues a narrowing of the capillaries, accompanied by a thickening of endothelial cells, occurs only in the complete absence of an active circulation. The closure of the vessels and obliteration of the lumen develops slowly over a period of fifteen to twenty minutes or longer. With the opening of the precapillary sphincters the diameter of the narrowed capillary returns almost immediately to its original tonic state. Under pathologic conditions in which capillary tone is diminished such vessels undergo considerable vasodilation when an active circulation is present [*32*].

In normal tissues, with contraction of the precapillary sphincters, the forward movement of blood ceases and then the cells gradually drain into the effluent venous channels, leaving the capillaries filled only with plasma and occasional platelets. When the venous vessels also contract, blood stagnates in the capillaries which remain open. It is only in exceptional circumstances—hypersensitivity, bacterial endotoxemia, cold—that the venous vessels narrow while the arterial inflow remains open [*33*]. Under these conditions many previously inactive capillaries are opened and the petechial hemorrhages develop around the postcapillaries and collecting venules. When venous spasm develops in conjunction with local tissue damage, capillary stasis sets in with unusual rapidity.

Smooth Muscle Tone. In assessing the current status of our knowledge of the activity of vascular smooth muscle, emphasis must be given to the considerable overlapping of regulatory mechanisms in the peripheral circulation. Fundamental to the entire problem is the recognition of factors which contribute to the basal tone of the smooth muscle cell. The term "basal" is used here to define the tone at a cellular level which exists independent of vasoactive influences. This is in contrast to its usage in certain physiologic experiments [*34*] in which it indicates the tone which remains when the vessel is cut off from its neurogenic influences (by either pharmacologic or surgical means). Humoral agents, such as the adrenal corticosteroids, have been shown to play an important part in the maintenance of cell tone *per se* [*35*]. Obviously, certain metabolic processes must be sustained by the smooth muscle cells in order to provide energy and to permit the specialized contractile mechanisms to reconstitute following repetitive stimuli [*36*]. Unfortunately, our knowledge of this important aspect of smooth muscle activity is extremely meager.

Superimposed on this basal state are influences of humoral and neurogenic origin which tend to modify the muscle tone [*24*]. There are two broad categories, those which are present continuously and thereby serve to reinforce the

intrinsic tone of the muscle cell and those which are introduced at intervals as a means of eliciting a particular type of response. Following surgical denervation most vascular beds exhibit a residual tone which differs in particular regions. The residual tone can be then shown to depend on humoral blood-borne principles. It is interesting to note in perfusion experiments that some tissues show a basal tone which is sufficiently high to produce a pronounced vasospasm upon surgical removal (ear), whereas in other tissues (hind limbs) the resultant tone is minimal and excision leads to vasodilation [*37*].

The term "critical closing pressure" has been introduced [*38*] to explain the abrupt change in the pressure-flow relationship in isolated perfused systems when pressures below 40 mm. Hg are reached. Direct visual evidence has not been provided to substantiate the existence of critical pressures in the intact microcirculation below which the terminal arterioles and precapillaries shut down. There is little doubt that the precapillary sphincters are unstable and have a tendency to shut down completely at periodic intervals. The metarterioles show only a moderate narrowing and gradual reopening, referred to as vasomotion.

In the case of the precapillaries, the mean diameter of the open vessel is apparently dependent upon the prevailing muscle tone, which varies under different conditions and in different tissues. In vessels whose muscle tone has been diminished by local tissue activity or injury, the precapillaries no longer open and close spontaneously. On the other hand, under conditions of general stress not only the precapillaries but the arterioles shut down completely.

VASCULAR REACTIVITY

Perhaps the single, most important feature which enables this segment of the circulation to function independently of the remainder of the system is the extreme sensitivity of the metarterioles and precapillaries to humoral constrictor and dilator agents. The microcirculation is unusually reactive not only to blood-borne vasoactive materials but to agents released locally within the tissue. There is good reason to believe that the increased sensitivity may be associated with the gradual lessening of neurohumoral control and with the predominance of local vasoactive products. For example, the arterioles, which are well supplied with nervous connections, are less reactive to constrictor and dilator agents than are the metarterioles and precapillary sphincters. The latter vessels are invariably the most reactive components and, in situations in which reactivity levels become increased or decreased, are the first to exhibit these changes [*39*]. The muscular venules on the effluent side of the bed are the least reactive constituents of the microcirculation to constrictor agents such as epinephrine (E) or norepinephrine (NE), although they are highly susceptible to tissue agents such as 5-hydroxytryptamine (5-HT) or histamine. Under normal conditions the precapillaries and metarterioles are the earliest vessels to react to humoral mediators, arterioles and venules participating actively only at concentration levels five to ten times higher than the threshold values for the smaller blood vessels. As indicated in a subsequent section, the gradient of reactivity can be distorted and even reversed by biological agents and experimental factors. This type of imbalance will have serious consequences on the capillary circulation and frequently accompanies local tissue or capillary damage [*40*].

Although measurements of threshold levels of reactivity provide a definitive index of the functional state of the smooth muscle cells, they are by no means complete representations of the capacity of the smooth muscle to respond to stimuli. Vessels which are refractory to E may still respond in a normal manner to other vasoactive agents. Likewise, the development of hyperreactivity to amines, such as E or NE, is not always accompanied by a shift in the response to other pressor materials [*39*]. During the irreversible phase of shock, the muscular components of the mesenteric microcirculation frequently become refractory to E and NE, but continue to react well to angiotonin or pitressin® [*41*]. As another example, the vascular bed of the skin during reactive hyperemia becomes refractory to E and NE but retains the capacity to respond to other constrictor agents [*32*].

Most studies on vascular reactivity have emphasized the capacity of different agents to induce a constrictor or dilator response [*42*]. Our own studies have brought to light the fact that profound alterations in blood flow can be introduced by a wide variety of biological agents which alter the state of responsiveness of smooth muscle to mediators either of blood-borne or of tissue origin [*43*]. Thus, in the face of a continuous tonic stimulus operating by way of the sympathetic nervous system, a greater or

lesser contraction of the smooth muscle elements can be established by agents which alter the reactivity of the effector unit.

It has been shown that the smooth muscle elements in the capillary bed can change their threshold of reactivity both on a general, nonspecific level, as well as in relation to particular agents [*43*]. As is well known, the dose-response characteristics of the vascular musculature in different tissues are not uniform and indeed may follow a diametrically opposite course, as in the case of E acting on the vessels of the coronary circulation or in skeletal muscle.

Reactivity changes constitute an important regulatory feature with respect to local readjustments to tissue metabolic needs. Numerous examples can be cited in this regard. Thus, the response of vascular smooth muscle to E or NE can be enormously increased or completely abolished by agents which themselves have no effect on smooth muscle contraction. Included in this category are SH-compounds, such as ferritin [*44*], polysaccharides such as the bacterial endotoxins [*40*], polypeptides produced by the kidney [*46*] and amines such as 5-HT [*47*]. Presumably these agents exert their effect through an interference with the inactivation of mediators such as E or NE, and/or by a competitive type of action on cell receptors. Although histamine has been shown to have a profound effect on the microcirculation, the precise role of this amine in the regulation of blood flow remains uncertain [*48*].

It is useful at this point to examine some of the experimental conditions which lead to increased or decreased states of reactivity, as a means of increasing our understanding of the mechanisms which govern the functional behavior of the small blood vessels.

In tissues exteriorized for microscopic study, the most common factor leading to an increased vascular reactivity is the sensitization of the smooth muscle elements by repeated exposure to above-threshold doses of E or NE. Under these conditions hyperreactive responses are obtained, not only with these mediators but with other vasoactive agents including direct stimulation with microneedles or microelectrodes [*49*]. A possible explanation for this situation would be the building up of a high intracellular concentration of these amines, as postulated by Houssay [*50*].

Stimulation of the sympathetic nervous system, either directly or indirectly, leads to a spectacular rise in reactivity of the small blood vessels. Thus, during asphyxia or shock, compensatory vasoconstriction is accompanied by a heightened reactivity to E or NE and an exaggerated vasomotion [*51*]. Inasmuch as generalized stress situations of this kind obviously involve the secondary release of humoral agents, the contribution of the sympathetic nervous system *per se* is not clearly established. More convincing evidence is derived from studies [*52*] in which direct electrical stimulation of the peripheral stump of the greater splanchnic nerve was shown to result in hyperreactivity of the mesenteric vascular bed, in conjunction with high titers of a blood-borne potentiating material. Identical patterns of hyperreactivity were obtained in animals which had been adrenalectomized. In view of the incomplete innervation of the terminal vascular bed, the evidence favors the local release of vasoactive material, possibly in the form of 5-HT from depots such as the mast cells.

The production of hypertension by various procedures which interfere with circulation of the kidneys, has led to the discovery of a number of vasoactive products which apparently arise as a consequence of renal hypoxia. These include the polypeptide angiotonin [*53*], VEM (a mixture of polypeptides) [*54*] and the sustained pressor principle (related to angiotonin) [*55*], all of which can be elicited by both acute and chronic stimulation of the kidney. In view of the high percentage of the total cardiac output which flows through the kidney, it is likely that under normal circumstances these substances are concerned with autonomous regulation of the intrarenal circulation. Their participation in general homeostatic phenomena must remain, in the light of our present knowledge, speculative.

There is increasing evidence [*56*] that amines of the 5-HT type can be released locally by a diversity of factors, including pressor agents, hypoxia, ischemia, etc. The widespread distribution of 5-HT and its biological activity at extraordinarily low concentration levels, supports its suggested importance in local vasoregulation. For example, Thomas and co-workers [*57*] have found that 5-HT, like bacterial endotoxins, sensitizes the precapillary arterioles and muscular venules to the vasoconstrictor action of E and NE, and that mixtures of 5-HT and E are capable of precipitating a skin lesion equivalent to the local Shwartzman reaction produced by bacterial endotoxins.

Several separate lines of investigation have pointed to an abnormal distribution of electrolytes between the smooth muscle cell and the extracellular compartment in different forms of vascular pathology. Thus, hyperreactivity in association with a hypertensive state can be induced by the chronic administration of steroids and sodium chloride [*58*]; potassium depletion by dietary restriction leads to a loss of vascular hyperreactivity in animals rendered hypertensive by renal manipulation [*59*]; and the aortas of animals with experimental hypertension show a significantly higher content of potassium than those of control animals, presumably in the muscle elements [*60*]. It is of interest to note that the local application of potassium salts (0.5 to 1.0 per cent), or an increase in the concentration of potassium chloride (0.6 to 0.8 mg. per ml.) in the physiologic medium bathing exteriorized tissues, leads to an enhanced reactivity to E, NE and to stimulation with microelectrodes, and renders the small blood vessels unusually reactive to fluctuations in temperature.

An interesting set of reactions, which may have bearing on the mechanism of vasospasm in general, are the effects of lipopolysaccharide extracts of gram-negative bacteria (so-called endotoxins) on the microcirculation studied *in vivo* and on preparations perfused *in vitro*. Small doses of endotoxin have been shown [*33*] to sensitize the blood vessels to E and NE, while larger or lethal doses lead to hyporeactivity and complete relaxation of the muscular vessels. *In vitro* studies [*61*] of arterial strips following sensitizing doses of endotoxin reveal a defect in the relaxation phase of the contractile process which permits successive stimuli to summate their effect and achieve a response approximating the staircase phenomenon. This is in contrast to normal vessels—repetitive stimuli do not lead to a sustained contraction and may actually result in a diminished response, particularly if the successive stimuli are superimposed during the relaxation or recovery phase of the contractile process.

Areas suffering tissue injury show a marked increase in blood flow. Damage sufficiently severe to lead to disruption of vessels and stasis will bring in its wake a deficient capillary circulation and tissue necrosis. It is generally conceded [*62*] that the local hyperemia here results from the release of vasodilator metabolites. Direct observations show that the vasodilation which accompanies tissue damage goes through two phases [*63*]. Initially, the feeding arterioles dilate so that the capillary circulation becomes extremely rapid. During this phase the precapillaries and metarterioles show an increased reactivity. Subsequently, the terminal vascular bed becomes unreactive, vasomotion is suspended, and all the precapillaries show a complete loss of tone.

VASOMOTION

The fluctuations in blood flow characteristic of the normal circulation are related to an irregularly recurrent series of partial contractions and relaxations of the metarterioles and precapillary sphincters at intervals varying from thirty seconds to as long as several minutes. This intermittent activity, which has been termed vasomotion [*64*], does not appear to be related to the vasomotor activity of the larger arteries and arterioles. Nor is there any comparable sequence of changes in the venules. The pattern of vasomotion can vary from complete absence, on the one extreme, to an extraordinarily rapid series of contraction-relaxation cycles. With augmented vasomotion, the frequency of the cyclic changes is increased, usually with the constrictor phase becoming increasingly apparent. With a depressed or impaired vasomotion, the number of cycles is diminished and the dilator phase becomes progressively dominant. It can be readily appreciated that changes of this character will have a profound effect on the rate and volume of capillary blood flow, and on the number of vessels containing an active circulation.

The vasomotor activities responsible for the intermittent nature of the capillary circulation have been shown to be influenced by both neurogenic and humoral factors. Vasomotion, although modified, persists in areas which have been subjected to surgical denervation [*65*]. Although it is difficult to be certain that all nervous connections have been removed by a given surgical procedure, the facts indicate that the vasomotion in part represents an intrinsic property of smooth muscle under the control of humoral agencies. The evidence as a whole relegates the activity of the sympathetic nervous system with respect to spontaneous vasomotion to that of a modifying influence, rather than a primary regulatory mechanism.

The loss of spontaneous vasomotion is associated with a number of important consequences. The blood is now distributed throughout the capillary system continuously, providing

a greatly increased surface for blood-tissue interchange. In instances in which the feeding arterioles are dilated, this condition will lead to an over-all elevation of the hydrostatic pressure in the capillary system and may eventuate in edema. There is also evidence of an interference with the return of blood from the capillary bed into the collecting venules. Active vasomotion seems to serve as a positive influence in maintaining an effective venous outflow. In the absence of vasomotion, the reduced venular flow may actually lead to an increased venous resistance and thereby serve to elevate the capillary pressure.

PLASMA SKIMMING

Some comment should be made on the phenomenon of plasma skimming and its effect on the general capillary hematocrit. The abrupt branching of the precapillaries provides a rather narrow orifice leading into the capillary network. Although the sphincters are invariably completely open or closed in their vasomotor activity, the extent to which the vessels open depends upon the tone of the smooth muscle. Thus, in the precapillaries which are distributed by the arterioles or by the most proximal portion of the metarterioles, the entrance into the branch is frequently such that the capillaries contain comparatively few blood cells. Further distally, where the side branches are about the same caliber as the parent stem, the flow into them is not appreciably hindered. In most instances the precapillaries exhibit plasma skimming for relatively short periods. The red blood cells are sufficiently elastic to be forced through orifices which are as narrow as 3 to 4 microns. When the precapillary orifice is smaller than this value there usually is no evidence of flow into the offshoot.

The arrangement of the vessels in most tissues is such that the precapillary branches, which are distributed directly from the arterioles and proximal metarterioles, return to the venous system ahead of the capillary branches which are distributed further distally. As a consequence, the larger collecting venules are continuously receiving comparatively low hematocrit blood in contrast to its tributaries which are formed by the confluence of the distal capillaries. This relationship is disturbed in situations in which vasomotion no longer exists. The possibility arises that dilation of the proximal precapillary sphincters will interfere with the effective return of blood from the capillary network and may actually give rise to an elevated intracapillary pressure. There is a need for information concerning the effect of vasoactive agents on this facet of capillary activity.

ARTERIO-VENOUS SHUNTS

The literature contains numerous references to the variety of pathways by which blood can return to the venous system from the tissues. Anatomic shunts of considerable size between arteries and veins have been demonstrated in the skin [*66*], in the intestinal wall [*67*] and in certain specialized structures [*68*]. More recently, consideration has been given to the possibility that some type of shunting mechanism exists in the kidney [*69*] in the liver [*70*] and in skeletal muscle [*71*]. All these organs have in common the need at certain periods to bypass the capillary circulation. There is a good deal of indirect information to support the existence of such pathways, although anatomic evidence has not as yet been provided. There is little doubt that occasional shunts between arteries and veins exist in almost every tissue of the body. Such shunts are not a prominent feature of most tissues. However, as the arterial tree subdivides to form the terminal vascular bed, direct communications between arterial and venous vessels become more frequent [*72*]. It is difficult to ascertain the extent to which such interconnections are a regular feature of the microcirculation. Many pathways, which lead from the arterial to the venous side of the system, provide ample opportunity for blood to bypass the major portion of the capillary network, despite the absence of anatomically distinct shunts.

The existence of discrete shunts presupposes separate regulatory mechanisms for diverting the blood through these structures [*73*] The seemingly indiscriminate arrangement of the shunts in the microcirculation makes it difficult to provide evidence for such regulatory mechanisms. On the other hand, it may be possible that interference with the capillary circulation, either through selective vasoconstriction or diminished venous outflow, will create mechanical conditions which favor the diversion of blood away from the capillaries into channels of least resistance.

VENOUS OUTFLOW

Tributaries of the venous system within the capillary bed consist of comparatively wide postcapillaries (20 to 30 microns in diameter)

which have no demonstrable smooth muscle and are invested with a prominent perivascular sheath. Smooth muscle cells appear only after the collecting venules are about 40 to 50 microns in size. Under normal circumstances the collecting venules and small veins are the least reactive components of the microcirculation [*32*]; they exhibit no spontaneous vasomotion and respond poorly to vasoactive agents. For example, the precapillary muscle elements usually respond with complete contraction to the topical application of E in concentrations of 0.1 to 0.2 μg. per ml., whereas the venules require about 2 to 3 μg. per ml. of E to elicit a partial narrowing.

The collecting venules, which are the most frequent site of blood cell extravasation and petechial formation [*74*], are the least distensible constituents of the peripheral vascular tree. The muscular venules, on the other hand, show a considerable range of variations in caliber, particularly during periods of hyperemia.

Under abnormal circumstances, the muscular venules become highly reactive to the extent that they exceed even in the arterioles and precapillaries in their response to both neurohumoral and metabolic factors. Thus, following the administration of bacterial endotoxins, during antigen-antibody reactions, and different forms of hypersensitivity [*75*], the venules react strongly to vasoconstrictor agents and frequently exhibit vasospasm. In acute conditions of stress, such as occur with hemorrhage or asphyxia, the venules become unevenly narrowed and fail to relax even after the arterioles and precapillaries have again opened up. In these situations the venules are also abnormally sensitive to fluctuations in temperature, a shift of as little as 2 to 3°C. leading to protracted vasospasm.

It is well known that the state of venous outflow will have a considerable effect on the capillary circulation. For example, in perfused preparations, it is possible to adjust the intracapillary pressure [*76,77*] by manipulation of the venous outflow. There is no clear evidence concerning the extent to which a comparable effect is introduced within the capillary bed by the initial tributaries of the venous system. It would appear that the collecting venules and muscular venules in the intact circulation do not represent major determinants in this regard. The interlocking character of the microcirculation on both the arterial and venous side in such structures as skeletal muscle and the intestinal wall tends to minimize the importance of venous resistance *per se* on capillary pressure and flow. However, in other tissues, in which the arterial circulation joins the venous system by more direct routes, the state of the effluent vessels may serve as an important regulatory adjuvant.

VASOACTIVE AGENTS

The influence of local tissue metabolites on the behavior of the microcirculation has been attributed to a vasodilator action of the locally elaborated agents. For example, it has been postulated that the neurogenic tone imparted by the sympathetic nervous system is antagonized by local metabolites [*62*]. This simple statement of fact probably represents an oversimplification. Locally elaborated agents must diffuse through the tissue in order to reach the effector cells of the blood vessels. Actually, the only vessels available to such local chemicals are the metarterioles, the precapillaries and possibly the venules. Some of the material may reach the larger venules by drainage into the blood circulation. However, the muscular arterioles, being comparatively thick-walled, are insulated from the surrounding tissue environment and are not readily affected by agents reaching them by diffusion. When local metabolites alter the response of the feeding arterioles, the effect therefore must be mediated by some indirect mechanism, either through neurogenic pathways, or through purely physical forces operating in retrograde fashion from the capillary circulation. Such considerations would make it appear that the widespread vasodilation which occurs during local hyperemia involves more than a direct effect of accumulated metabolites on the muscular capillaries, as postulated.

The combined effect of mixtures of several vasoactive agents frequently is greater than that of the agents acting singly. Here again we are faced with a situation in which it is difficult to establish whether or not a new parameter of cellular metabolism is being altered when several vasoactive materials are acting simultaneously. Recent experiments [*57*] have shown that mixtures of 5-HT with E produce a substantial change in vascular reactivity, which in association with extensive damage to blood capillary endothelium leads to the destruction of these small blood vessels.

RELATION OF MICROCIRCULATION TO CHANGES IN BLOOD PRESSURE

Although chronic situations leading to disturbances in systemic blood pressure are in many instances believed to be related to changes within the microcirculation, there is no clear-cut indication of the precise means by which this end-result is achieved. Under normal circumstances the blood pressure is maintained by receptor elements, in and around the heart and its associated blood vessels. These mechanisms operate by way of the vasomotor center to influence cardiac output and peripheral vasoconstriction. Actually, changes in blood pressure are monitored without reference to the adequacy of blood flow within the tissues. Inasmuch as the pressure is maintained within a comparatively fixed range, the implication here is that changes in the circulation through the capillary bed ordinarily have no direct influence on the systemic blood pressure, and as such require only local regulation. It is only in situations in which the blood flow remains inadequate for protracted periods that the resulting biochemical changes release into the blood stream products which will influence the vasomotor center and other centrally located receptors.

Hypertension. It therefore becomes difficult to support the assumption that vasoactive agents, which primarily lead to a disturbance within the capillary bed proper, will lead *per se* to an altered blood pressure. Inasmuch as these vessels are distal to the major seat of peripheral resistance, the terminal arterioles, homeostasis requires that some changes be induced in the arterioles, either as an adaptive measure or as a direct consequence of the change in the capillary circulation. This line of reasoning leads to the possibility that in the early stages of experimental renal hypertension the arteriolar changes are adaptive measures which are reversible [*78*]. Later, with the persistence of a defect in the microcirculation, changes may develop in the arterioles which would be relatively irreversible. It is therefore suggested that the instigation of changes in the microcirculation by vasoactive principles sets into motion effects on the terminal arterioles which are both musculotropic and neurogenic. It is possible that hypertension in man develops as a consequence of disturbances in this over-lapping area of systemic and local regulation of the arterioles. The extent to which such changes become permanent will differ in the various tissues of the body, depending upon the capacity of local mechanisms to compensate for the altered hemodynamics.

Hypotension. The state of shock, induced by hemorrhage, trauma, or endotoxins, is essentially a collapse of the peripheral circulation, resulting from an interference with the intrinsic behavior of the microcirculation. Vasodilation, loss of spontaneous vasomotion, hyporeactivity, loss of endothelial tone and increased capillary permeability have been reported with different experimental procedures [*79*]. Inasmuch as there is no clear-cut evidence for a failure of neurogenic regulation [*80*], the circulatory insufficiency would appear to be the result of humoral principles of either local or systemic origin. In traumatic and burn shock, a variety of tissue breakdown products, such as adenyl compounds and H-substances, have been made suspect [*81*]. In the case of shock induced by protracted hemorrhage, bacterial factors of enteric origin [*82*] and vasoactive byproducts of stagnant hypoxia (ferritin) [*54*] have been shown to have a profound influence on the behavior of the microcirculation. The majority of the tissue breakdown materials produce their effect by dilation of the feeding arterioles. Products of stagnant hypoxia, such as ferritin, act through a vasoinhibition of the terminal arterioles and precapillaries. Bacterial factors, such as the endotoxin of gram-negative bacteria, affect, not only the reactivity of the muscular vessels in the microcirculation but the integrity of the capillary wall [*45*]. There is persuasive evidence that the pathologic manifestations of bacterial endotoxins are to a considerable extent mediated through an effect on the local mechanisms for handling E and NE. Recent observations [*57*] suggest that local tissue changes in flow under these conditions are the result of the release of 5-HT and its interaction with E inactivating systems. E in combination with 5-HT has a cytotoxic action on vascular endothelium, pointing to the importance of the metabolic effects of these amines [*83*] on cells other than smooth muscle.

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Oxygen Tension of Peripheral Tissue*

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A THOROUGH understanding of diseases of the peripheral circulation depends upon knowledge of the basic causes of the diseases, but these at present are little understood. The immediate study of peripheral ischemia is chiefly concerned with three biologic variables: the need of peripheral tissues for nutritive factors, the supply of these factors, and infection. The approach to the first of these variables, the tissue needs, has been largely by means of *in vitro* measurements, usually by the Warburg technic. The second of the variables has for many years been under investigation by various methods of measurement of peripheral blood flow. The third has responded remarkably to the application of chemotherapeutic and antibiotic agents. Any new method that promises further correlation of the first and second of the three variables deserves exploration.

All tissues have varying metabolic needs and varying supplies of nutrients. The metabolic rates correspond with the rates of utilization of oxygen if essential substances are present in proper concentrations. Temperature affects both the demand for and the supply of oxygen; demand in that metabolism increases with temperature, supply in that oxygen dissociates more completely from hemoglobin, and vessels usually dilate when temperature is increased. Otherwise the supply corresponds with the volume of normal arterial blood delivered to a unit volume of tissue in a unit of time. The supply depends on delivery of blood through capillaries, upon the diffusion constants of the tissue, and upon diffusion gradients from the capillaries to tissue. Discrepancies between supply and need of oxygen appear as changes in concentration and in tension of oxygen in the tissue, since oxygen is intimately concerned in most metabolic processes of mammalian tissue, and oxygen is probably more rapidly depleted than any other substance in the blood unless it be acetylcholine. It is true that tissues tolerate very wide ranges of oxygen tension, but when oxygen can be measured in the tissue an opportunity is provided to estimate decreases in other essential substances. Furthermore, very low tensions of oxygen limit metabolism, and very high tensions can be toxic, so an approach to either extreme is a sign of danger that should not be ignored.

In general, studies of the immediate problem in diseases of the peripheral circulation deal with normally elaborated arterial blood. If another organ such as the kidney, liver, lung or heart is also diseased, the delivery of nutrient substances to the tissues, the removal of waste products, and the concentrations of interstitial substances will be complicated and the concentrations of substances surrounding the cells will be altered. Cellular activity will be affected. Even without these complications, disease of a single end artery can cause a fundamental change in cellular environment and can prevent optimal cellular activity. If, in addition, some of the ischemic tissue is traumatized or infected, and this is a common clinical situation, metabolic needs are increased or otherwise altered: the integrity of the tissue may be further endangered. Any measure of the resultant change in supply or demand, made by an *in vivo* method, would presumably provide useful information in peripheral vascular disease. We believe that the polarographic technic for *in vivo* determination of oxygen tension is such a method. This method is less commonly, although probably more properly, termed the amperometric method [*1*].

Attempts at measuring oxygen in tissues are as old as those for measuring blood and other body fluids [*2*]. In general, the old method consisted of injecting a "bubble" of a respiratory gas mixture into the tissue, allowing time for equilibrium with the oxygen in the tissue, and then removing a sample of gas and analyzing it for oxygen [*3–6*].

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However, even the most advanced development of this technic, that of Bazett and Sribyatta [*7*], has a lag of one hour. As a consequence, the gas bubble technic has afforded little dynamic data. The first practical technic for measuring rapid changes in oxygen in tissues is the amperometric method, utilizing the open-tip metal electrode. The response of the electrode is practically instantaneous. The size of the electrode usually used is about that of a 25 gauge needle. Its one serious disadvantage is the difficulty of calibration. It has already provided information regarding changes in oxygen in human skin and muscle, and has demonstrated that some of the old concepts are unfounded [*8*]. It is still a research instrument, but holds promise of being a tool for diagnostic and therapeutic problems.

GENERAL APPLICATION

The method measures the rate of delivery of oxygen to the electrode. In a solution it measures the delivery of oxygen occasioned both by the tension of oxygen in the solution and by any motion of the fluid in respect to the electrode; any convection current will influence the readings. Most of the early development of amperometric titrations was by use of the dropping mercury electrode. That type of electrode has advantages in the measurement of many ions in free solutions, but in the analysis of oxygen it is no more useful than the solid metal electrode. Furthermore, solid metal is required for insertion in tissues. If the diffusion constant of the tissue remains unchanged, the platinum electrode can be used to estimate oxygen tension, in mm. Hg, and to measure percentage changes in oxygen tension. Some authors refer to the measurement in tissues as being one of "oxygen availability" [*9,10*] rather than of "oxygen tension," and this is probably wise when no attempt has been made to calibrate the electrodes in that tissue. The measurement is not one of blood flow, but it sometimes gives information about changes in blood flow. The oxygen tension of arterial blood usually remains fairly constant when the gases inhaled are unchanged; when oxygen utilization by the tissue also remains constant, any large change in oxygen tension of tissue can be attributed to change in blood flow. However, smaller changes in the readings could result from temperature changes unless corrections are made for the temperature coefficient of the diffusion current [*1,8*]. Furthermore, it might be difficult to detect even great variations in blood flow at the upper range of flow through a tissue that uses little oxygen. Changes in the flow of blood solely through arteriovenous anastomoses probably would not be detected, since arteriovenous anastomoses are not well designed for the transfer of oxygen, or of other substances, between blood and tissues. This may allow a special use of the electrode, in conjunction with the conventional methods of measuring blood flow, in estimating the proportion of blood that passes through anastomoses and through capillaries. Quantitative methods for measuring blood flow do not distinguish between circulations with and without direct interchanges between blood and tissues.

The electrode can be used to furnish a reasonable estimate of the metabolism of an intact tissue. If the circulation to tissue is arrested by an arterial tourniquet, the rate of decrease of oxygen tension is a function of oxygen utilization. Furthermore, an estimate can be made of the oxygen stored in the erythrocytes in the minute blood vessels by comparing this rate of decrease of oxygen tension with that which results when the tissue is blanched by pressure [*8*]. The rate of decrease is much more rapid with blanching than it is when the tourniquet is used: the difference in rate is a measure of the local storage of oxygen in red cells compared with that in the rest of the tissue.

This presentation is not primarily concerned with the central circulation. However, central alterations in the arterial blood influence peripheral tissues, and it seems not amiss to describe the conditions under which alterations of arterial oxygen may be detected by changes in oxygen tension measured in a tissue. To date this can best be done in skin [*11*]. During cutaneous vasodilatation the blood flow in skin greatly exceeds that needed to supply the metabolic needs of this organ. This excess is required in the regulation of body temperature. Indeed, venous blood from a resting arm during cutaneous vasodilatation is highly "arterialized"; its concentration of oxygen is nearly that of the arterial blood [*12*]. Some of the excess circulation passes through arteriovenous anastomoses [*13*], but judging from oxygen electrode measurements much of it passes through capillaries. That is, the oxygen measured by the electrode is in the tissue. Most of the tissue's supply of oxygen comes via the capillaries rather than through arteriovenous anastomoses. The oxygen tension of skin is low during cutaneous vasoconstriction. When cutaneous vasoconstriction gives way to vasodilatation, whether reflexly or by direct heating, the

cutaneous oxygen tension increases conspicuously [*8,14*]. This increase would not be expected from an increment in flow solely through the arteriovenous anastomoses. Moreover, changes in oxygen tension of vasodilated skin can be estimated from changes of oxygen content of arterial blood by use of the conventional oxyhemoglobin dissociation curve [*15–17*]. (Fig. 1.) This would not be so if the oxygen tension of such skin were much different from that of the arterial blood. Furthermore, at least by roughly calibrated measurements, the oxygen tension of vasodilated skin is found to approximate the value given for arterial blood [*8*].

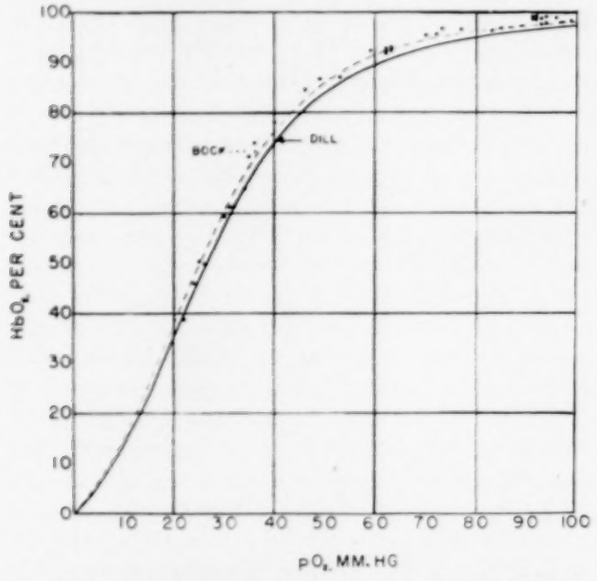


FIG. 1. An oxyhemoglobin dissociation curve of blood [*17*]. The vertical ordinate expresses per cent saturation of hemoglobin with oxygen; the horizontal, oxygen tension of the blood. The points along the curve are from *in vivo* measurements of Lambertsen et al. [*17*] at observed pH and oxygen tension. The solid curve is from Dill at a serum pH of 7.40, the dotted curve is from Bock, Field and Adair at a CO_2 tension of 40 mm. Hg.

Therefore, changes in the oxygen tension of arterial blood can be closely followed by polarographic measurements of oxygen in vasodilated skin. When arterial oxygen tension is high, as when pure oxygen is inhaled, the measurements are more sensitive than are direct measurements on samples of arterial blood by conventional methods.

EQUIPMENT AND TECHNIC

The electrode we have used in human skin consists of a bare, slightly pointed tip of a 0.2 mm. platinum wire. It is insulated above the tip by soft glass. The electrode for use in muscle is made of 0.4 mm. platinum, 11 per cent ruthenium alloy wire exposed for 0.5 cm. length, the rest of the wire being insulated with many coats of a polymerized plastic. The electrode for skin is inserted 1 to 2 mm. at a 45° angle and its upper portion is supported on a cotton ball by means of 1 cm. wide adhesive tape; the electrode for muscle is inserted deeply enough to require no additional support. The usual electrical circuit includes the electrode (cathode), a selector switch for bringing other electrodes into the circuit, a main switch, an Ayrton shunt, a 1.5 volts dry cell, fixed and variable resistances, a sensitive beam galvanometer and a salt bridge connected to a calomel half-cell. (Fig. 2.) When the electrode has been inserted in the tissue, a finger is placed in the salt solution, an EMF of −0.6 volts is imposed and the main switch is closed, the circuit is completed; the current that flows

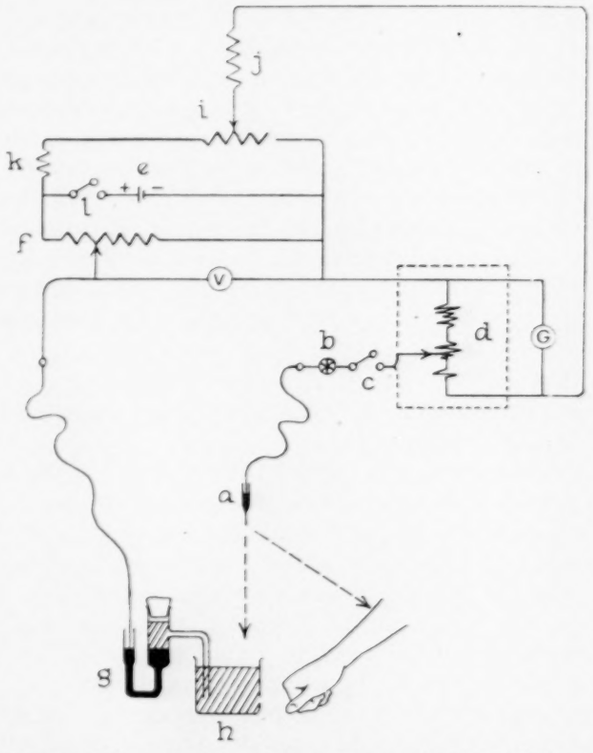


FIG. 2. Circuit for use of the oxygen electrode with a galvanometer. (a) Electrode tip (cathode), (b) selector switch (controlling six electrodes), (c) electrode switch, (d) Ayrton Shunt (Rubicon No. 1243), (resistance 0 to 65,000 ohms), (e) dry cell (1.5 volts), (f) variable resistance (500 ohms), (g) calomel half-cell (anode), containing 0.9% NaCl, (h) 0.9 per cent NaCl in beaker, (i) variable resistance (10,000 ohms), (j) fixed resistance (2,000,000 ohms), (k) fixed resistance (40,000 ohms), (l) main switch, (G) galvanometer (Rubicon No. 3418), (V) voltmeter [*8*].

bears a straight-line relationship with oxygen tension in the tissue [*8*]. If a smaller electrode is used than that described for skin, an electronic circuit should be employed because the changes in current with changing oxygen tension may be too small to be detected with a galvanometer. An electronic apparatus has the added advantage of lending itself to automatic recording.

For the most part, readings have been made after closing the circuit for a period of ten seconds timed by a stop-watch [*8*]. Two or more minutes are allowed to elapse between readings in order to permit oxygen to diffuse back to the surface of the electrode where it has been electrically reduced during closure. Longer times between closure are required when the circulation of blood in the tissue is very poor. Some studies have been made with constant closure of the circuit. After a minute or more the current decreases to a low plateau around which changes in current, caused by changes in oxygen tension, can be detected [*18*].

Even with the interrupted closure there is usually a slow downward drift of current during at least the first few readings. For this reason, it is well to have two "control" periods one before and one succeeding the experimental period in which changes of oxygen tension are being measured. The electrode should be kept in place in the tissue: if the electrode moves there is a change of current, usually an increase that results from the more rapid supply of oxygen from fresh tissue brought adjacent to it. The change may also result from dyshomogeneity of oxygen utilization and of vascularity of the tissue. It is therefore advisable to avoid comparisons of oxygen tensions measured with repeated insertions of the electrode unless many electrodes are employed and the mean of the readings is used.

Calibration of electrodes is not wholly satisfactory and is not always necessary. Uncalibrated electrodes may be used to gather useful information about changes in oxygen tension. If this is done the results are better expressed as per cent of initial, stable values, than as per cent of an extreme. In our attempts to calibrate electrodes in human skin we have found a 25 per cent error [*8*]. This error doubtless diminishes when numerous electrodes are used. In muscle, we have so far been unable to calibrate the electrodes. The calibration in skin consists of measuring the current that flows after the electrode is inserted in freshly dead skin in a solution of known oxygen tension. The oxygen tension of the skin is presumed to be that of the solution. The consistency of skin holds the electrode firmly, but the jelly-like structure of muscle permits movement of the tip thereby making calibration difficult. Corrections must be made for changes in temperature of the skin [*8*]. Using electrodes calibrated in this manner, the mean oxygen tension of healthy vasodilated skin, which has no interference with its blood supply, is about 90 mm. Hg. Since this figure closely approximates that of arterial blood, we think this method of calibration is probably justified. When pure oxygen is breathed the mean value is 4.5 times as great. If no oxygen were used by the skin or if the circulation were infinite the expected figure would be 4.8, since air is about 21 per cent oxygen. It might be as well to calibrate electrodes, after inserting them in intact vasodilated skin, by giving them calibration values based on the assumption that the oxygen tension of such skin closely approximates that of arterial blood, 90 to 100 mm. Hg. Living muscle, even resting muscle, appears to extract much of the oxygen eliminating the possibility of calibration in this manner [*19*]. An approximate calibration for use in muscle might be made in water or gelatin by using the diffusion coefficients available for these substances, water 0.51, gelatin 0.45 and muscle 0.31 [*20*]. However, diffusion distances may complicate such calibrations and it is better at the present time to report changes of oxygen tension of muscle in relative terms.

RESULTS

Even moderate *reflex cutaneous vasodilation* produced by body-warming increases oxygen tension [*8*]. This has been measured in the skin of the finger and toe, of the hand and foot, and of the leg and forearm. Corrections are made for the effect of changing temperature, already alluded to [*1,8*]. With further reflex vasodilatation there is further increase in oxygen tension. With "maximal" reflex vasodilatation one would expect that oxygen tension would reach a plateau. In general, our observations bear this out but a more complete study of the oxygen tension in relation to the whole range of cutaneous blood flow is in order. Conversely, reflex vasoconstriction, by body-cooling, decreases the oxygen tension [*8*]. During severe reflex vasoconstriction values may be reduced to a tenth of those during vasodilatation.

The rate of delivery of oxygen to the skin depends in large measure upon the degree of cutaneous vasodilation [*18*]. When oxygen is inhaled it can be detected by an oximeter within

about nine seconds as an increment in saturation of oxyhemoglobin in capillary blood. Chilling or warming the body has little effect upon this interval. In skin having a moderate degree of reflex vasodilatation an increment is detectable by the platinum electrode in twenty-five seconds (mean). In markedly vasoconstricted skin the increment is delayed to some sixty or more seconds.

Direct heating and cooling of the skin profoundly affect cutaneous oxygen tension, as well as cutaneous blood flow. This is true of the skin of the foot, of the pretibial area and of the thigh of normal and ischemic extremities [*14*]. The temperature of the air surrounding the leg was varied over the range 0°C. to 60°C. The resulting temperatures of the skin at the bases of toes, as measured by a covered thermocouple, ranged from 10°C. to 50°C. In normal limbs, oxygen tension reached a peak at 43°C. (mean) skin tempertaure and in ischemic extremities (arteriosclerosis obliterans) at 40.6°C. (mean); it was less at lower and at higher skin temperatures. When the temperature of ischemic limbs was raised, pain was experienced before oxygen tension declined. It appears that under direct heat a temperature is reached at which the increase in oxygen utilization (metabolism) outruns the increase in oxygen delivery occasioned by increases in blood flow and in dissociation of oxyhemoglobin. However, since pain may result before the critical temperature is reached, and substances other than oxygen may be involved, one cannot conclude that the desirable temperature for the ischemic limb is that which results in maximum cutaneous oxygen tension.

The rate of delivery of oxygen to the skin can be greatly increased by direct heating. When a normal extremity is heated in 47°C. water, and vasodilatation is maintained reflexly as well, inhaled oxygen is detected by the electrode in little over ten seconds [*18*].

Positions of the body: in general the passive dependent position of a limb increases the blood flow [*21*] and increases the oxygen tension of its skin [*22*] and of its muscle [*23*]. Further investigation may yield exceptions to this general statement. Recumbent patients with severe arteriosclerosis obliterans of the legs were studied while on a tilt table. When the foot of the table was lowered through 5 degrees, the oxygen tension of the skin at the base of the toes increased in twenty minutes by 13 per cent (mean), and in two hours by 22 per cent (mean) of that in the horizontal position. With these small changes in angle, changes in blood flow could not be detected and the oxygen tension of the skin of toes having normal circulation changed little: depression increased oxygen tension by 4 per cent (mean) and elevation had no significant effect. The effect of greater angles, for sustained periods, upon oxygen tension in skin of normal toes has not yet been studied. The studies of oxygen tension in muscle were made in normal subjects in the sitting position. Electrodes were placed in the muscles of the forearm. Marked decreases in oxygen tension were observed when the arm was passively raised from heart level to 35 cm. above heart level. Elevation of this degree greatly decreases blood flow in resting muscle [*23*].

Buerger's exercises were performed by normal subjects and by patients with severe arteriosclerosis obliterans of the lower extremities. Changes in oxygen tension of the skin at the base of the toes were observed [*24*]. No studies have been made on muscle. Patients started in the recumbent position for a sufficient length of time to gain a satisfactory baseline of oxygen tension and then alternately sat up with feet dependent over the side of the bed for three minutes, were recumbent for three minutes, sat again, etc., for several cycles. The positional changes were not wholly active, as in conventional Buerger's exercises, because the wires to the electrodes had to be protected by the investigator's hands upon the patients' legs and upon the wires. In normal subjects and in patients the oxygen tension during sitting increased by about 70 per cent (mean) of the value during recumbency. Little or no additional increment was gained by successive cycles. The temperature of the skin changed little, perhaps because of the known lag in skin temperature with changes in blood flow. It is possible that distention of capillaries, by greatly increased venous pressure, played a part on the more rapid delivery of oxygen to the tissues. However, when the capillaries of the recumbent subject were distended by this degree of venous pressure by means of a cuff inflated to 60 mm. Hg only slight, and bi-directional, changes in oxygen tension resulted.

An oscillating bed, when properly used, increases the oxygen tension of skin of ischemic limbs; the effect of such a bed on oxygen tension of the muscle of the limb has not been investigated. The increased oxygen tension in skin is at least in part a result of an increased flow of blood [*25*]. The bed is suspended at its center, its foot-end slowly falls while the head-end rises,

and vice versa. The effects of certain angles and timings of the foot-down position upon cutaneous oxygen tension and temperature (23°c. room) of the toes were studied. Twelve degree and 20° foot-down angles were maintained for times varying from twelve seconds to five minutes. In each cycle a brief foot-up angle of 5° was used, an angle sufficient to empty the veins. When the briefest foot-down position was used there was little increase in oxygen tension or of skin temperature. When the foot was left dependent for one or more minutes during each cycle considerable increases were produced. With the 20° angle for five minutes, in each cycle, the oxygen tension increased by 30 per cent (mean) and the blood flow was calculated from skin temperatures to change from 7 ml. per 100 ml. per minute to 13 ml. [*26*]. When a constant foot-down angle of 20° was used for forty minutes the increases in oxygen tension were of the same order of magnitude as those produced by oscillations to the same angle for five minutes. A constant foot-down position of long duration should probably be avoided because of edema and possible thrombophlebitis.

Some *drugs* have been shown to change the oxygen tension of the skin of extremities. Fewer studies have been made of muscle. Gabel has demonstrated that epinephrine administered intra-arterially in the intact dog, or into its perfused-denervated leg, causes a fall in oxygen tension of the skin and a rise in oxygen tension of resting muscle [*27*]. In man, epinephrine subcutaneously is known to decrease the oxygen tension of the skin [*19*]. No change in oxygen tension of the muscle was detected [*19*]. Intravenous administration of priscoline® (2-benzyl 4,5-imidazoline) and of ilidar® (azapetine) increase the blood flow [*28,29*] and oxygen tension [*19*] of human skin. In preliminary trials, with usual doses administered intravenously, the following failed to change the oxygen tension of human muscle: niacin, roniacol® (beta-pyridyl carbinol) and nicotine [*19*]. Intra-arterially injected histamine increases the blood flow and oxygen tension of the skin of limbs made ischemic by arteriosclerotic occlusion [*30*]. Further studies are needed. One would expect that any drug which relieves vasoconstriction will at the same time increase oxygen tension, especially when the initial vasoconstriction is intense.

Oxygen enters skin to some extent directly from the environment. Exposing a cyanotic, very ischemic limb to pure oxygen may relieve the cyanosis and lessen pain [*31*]. The direct effect of oxygen on the oxygen tension of such skin has not been studied but we have found the oxygen tension of the skin of a normal extremity to increase by such exposure, and when an arterial cuff is applied the oxygen tension decreases more slowly than when the limb is in air. Oxygen inhalation greatly increases the oxygen tension in normal vasodilated skin, and even in severe peripheral vasoconstriction and arterial occlusion, inhalation usually increases it at least a little [*8*]. It sometimes appears to relieve ischemic pain. Horwitz et al. find an increase in oxygen tension of 42 per cent (mean) in human skeletal muscle when pure oxygen is inhaled [*19*]. The direct application of oxygen and oxygen inhalation may find a place as an adjunct to the treatment of ischemic limbs. However, oxygen alone lacks the advantage afforded by proper positions, some physiotherapeutic procedures and vasodilator drugs, of increasing the blood flow and the supply of all the blood constituents required by the tissues.

SUMMARY

Changes in oxygen tension of living tissues *in situ* can be estimated by means of a small platinum electrode in a suitable electrical circuit. Many such studies have been made in normal human extremities, in which during cutaneous vasodilatation the cutaneous oxygen tension closely approaches that of arterial blood. In cutaneous vasoconstriction and with arterial occlusion the oxygen tension of the skin is reduced, sometimes to a small fraction of that in normal vasodilated skin. In ischemic extremities cutaneous oxygen tension can be increased by environmental oxygen, by inhaled oxygen and by various physical measures and drugs that increase the cutaneous circulation. There is some evidence that cutaneous oxygen tension can be made to change without concomitant changes in blood flow, perhaps because of changes in oxygen utilization or in the rate of delivery of oxygen through the capillary wall.

Fewer studies have been made on oxygen tension of muscle: these have been of resting skeletal muscle. In normal man oxygen tension of muscle rises when oxygen is inhaled and decreases with arterial arrest by a pressure cuff. Changes in oxygen tension of muscle with positional changes have also been demonstrated. The several drugs studied produced no measurable change in oxygen tension of human muscle. In the dog epinephrine appears to increase the oxygen tension of muscle.

Oxygen tension tends to reflect blood flow but the method measures the resultant of oxygen delivered through capillaries and utilized by the tissue rather than the total blood flow alone. More measurements, perhaps especially those of muscle, are needed in studies of the complex disorders incident to peripheral vascular disease.

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The Pathogenesis, Prevention and Medical Management of Peripheral Arterial Thrombosis*

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THROUGHOUT his entire existence man is poised delicately and dangerously as on the two-faced escarpment of a mountain. On one side are the risks of hemorrhage and on the other the deadly threat of thrombosis. By a remarkable combination of chemical and physical processes he almost incessantly and simultaneously has hemorrhages and thromboses, yet only rarely does he slip off his precarious perch to a catastrophic injury or end. The risk of death or disability from thrombus or embolus, hereinafter to be referred to as thromboembolism, is far greater than that of hemorrhage, and this summary will be concerned with thromboembolism as it occurs in the peripheral arteries.

What are the peripheral arteries? This is a matter of definition. While they are commonly considered to include those arteries which supply the extremities, the position may well be taken that they should include all arteries and their branches which are peripheral to the heart and aorta, including the pulmonary, renal and cerebral vessels. Some consider that the coronary arteries should also be included. While the present discussion will use the arteries of the extremities as examples, most of the conclusions, where appropriate, may be equally applied to other arterial systems.

Three primary considerations must be borne in mind when considering the pathogenesis of thromboses [*1*]:

(1) Blood is a constantly varying mixture of many components, some of which have undoubtedly not been recognized as yet. In any thrombosing process *in vivo*, most if not all of these components become involved and many of them play a dynamic role in the formation of the thrombus.

(2) In disease states the development of thromboembolic phenomena does not proceed in the orderly fashion suggested by any of the schematic outlines which have been developed for academic or symbolic purposes. All schematic presentations must of necessity be oversimplified; the whole process is enormously complex. Actually, at the same instant many stages of the process may be taking place—chemical, physical, physiologic and pathologic.

(3) The clotting tendency, as measured by clotting time or prothrombin activity as determined from blood drawn from one set of veins may bear little relationship to the clotting tendency in some other area of the vascular tree in which, for example, tissues may be undergoing serious changes as a result of trauma, infection or cancer. There should be no great surprise, therefore, when a patient has a hemorrhage in one area while he has a thrombosis elsewhere [*2*], or when thrombosis or hemorrhage occasionally occur while a patient is considered to be at the optimal level of anticoagulant therapy as measured by the usual tests of blood drawn from the antecubital veins.

The development of an arterial thrombus usually depends on: (1) changes in the wall of the artery which roughen the intima or narrow the lumen, as for example with atherosclerosis or thromboangiitis obliterans, (2) changes in physical and chemical constituents which lead to the deposition or concentration of fibrin in the local area, and (3) the adhesion of cellular and other particles to the wall, which then build up to narrow or totally block the lumen of the vessel.

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CHANGES IN THE WALLS OF THE ARTERIES

By far the commonest of the changes which ultimately end in thrombosis of a vessel are those which produce atherosclerosis. The laying down of excessive amounts of lipids in the intimal lining has been the subject of innumerable reports in recent years and will not be dealt with here. There are, however, some key questions which are still unanswered, among which are: (1) Why does atherosclerosis develop at vastly different rates in persons on similar diets? (2) Why does atherosclerosis fail to develop at an increased rate in some patients on high fat, high cholesterol diets? (3) Are apparent hereditary or familial tendencies toward early atherosclerosis actually due to familial eating or living habits rather than to the transmission of genes?

There seems to be little doubt that the female sex is protected, at least until after the menopause. Our early findings [*3,4*] in this area have recently been confirmed by many others [*5–7*]. While the questions listed are challenging as they apply to individual problems, we cannot ignore the strong evidence that fat intake which results in obesity is associated with increased atherosclerosis. Early atherosclerosis is also associated with elevated cholesterol levels in the blood as with xanthomatosis, diabetes mellitus, nephrosis and essential hypercholesterolemia. There has been a tendency to apply deductions regarding the development of atherosclerosis with or without hypercholesterolemia due to these metabolic diseases to the atherosclerosis seen in patients who do not suffer from them. Caution should be exerted not to take this inferential step without more evidence than is available at present. The questions related to the relative etiologic importance of saturated fats, unsaturated fats, linoleic acid and other factors are of the utmost significance but are not conclusively settled and are beyond the scope of this paper. Repeated local stress does appear to encourage the laying down of lipids, as can be observed, at least in this country, at almost every autopsy of patients over the age of forty. Inflammatory reactions such as are encountered in thromboangiitis obliterans, periarteritis nodosa and local infections produce irregular surfaces which also encourage thromboses. Trauma, whether accidental or surgical, may roughen the intima with the same result.

The next steps leading to thrombosis are extremely complex and far from fully understood. We are not certain whether or not the primary action may be physical rather than chemical. For example, it has been suggested that the inner surfaces of the tubes (arteries) may normally have negative (repulsive) charges which tend to keep the components of the blood from adhering to them. The natural anticoagulants, as exemplified by heparin, appear to have fairly strong negative charges. These may aid in keeping certain molecules, notably those of fibrinogen, in a state of mutual repulsion. When conditions change, reducing these negative charges, it becomes easier for the long, slender, rotating molecules of fibrinogen to adhere to each other, producing the sticky fibrin [*8,9*] which in turn may adhere to the injured wall of the vessel. This enmeshes other components of the blood, first platelets, which in turn contribute to this reaction by the release of thromboplastin which speeds up the production of more fibrin. Sheppard and others working in our laboratory [*10–14*] have explored this field for some years but much more needs to be done to clarify the physical aspects of this process.

More has been done by countless workers on the biochemical aspects of the coagulation process. Unfortunately most of this work had of necessity to be carried out *in vitro* under conditions which are foreign—although probably somewhat parallel—to those encountered within the walls of the vascular system. The following is a modification of several theories which have been evolved, notably that of Owren [*15*]:

(1) Contact with the surface of the wall initiates blood coagulation by (a) disintegration of platelets and release of platelet lipid thromboplastin factor, (b) activation of the antihemophiliac B factor (plasma thromboplastin component or PTC, Christmas factor), and (c) activation of proconvertin (SPCA, factor VII, co-thromboplastin, the stable factor).

(2) Tissue injury, such as already described, yields thromboplastin directly. In addition, *in vivo* destruction in other portions of the body due to cancer or severe infections may apparently increase the concentration of free thromboplastin. In the blood the platelet lipoid factor, the antihemophiliac A factor and the activated antihemophiliac B factor interact in the presence of calcium to produce thromboplastin.

(3) Thromboplastin and proconvertin (factor VII) combine to form convertin.

(4) Convertin, together with calcium, pro-

duces a minimal conversion of prothrombin to thrombin.

(5) This initially formed thrombin starts the accelerator system, i.e., the conversion of proaccelerin (factor V) to accelerin (factor VI).

(6) Convertin and accelerin interact in the presence of calcium to form prothrombinase (Factor VI?).

(7) Prothrombinase in the presence of calcium accelerates the conversion of prothrombin to thrombin.

(8) Finally, thrombin is formed in sufficient concentration to convert fibrinogen to fibrin.

Balanced against these interactions which move in the direction of coagulation are a series of inhibitor reactions which tend to inactivate thromboplastin, proconvertin, convertin, accelerin, antihemophiliac B factor, prothrombinase and thrombin. The action of the anticoagulant drugs in support of this inhibition, thus interfering with coagulation and thrombosing, will be outlined later in this paper.

The reactions described may appear to be complicated, but they actually represent a rather crude oversimplification of what actually takes place. Many new factors have been described—some of them may prove to be of importance, but where they fit into the picture is as yet not determined. The problem of communication has been greatly complicated by the understandable but confusing pride of parenthood in nomenclature exhibited by various workers in this field. As a result, most of the factors are known by multiple names, for example, factor VII has been known by some fourteen titles. A tower of Babel has thus been erected. An International Committee for the Standardization of the Nomenclature of Blood Clotting Factors is presently engaged in the difficult task of unscrambling the nomenclature and evaluating the claims for new factors.

The morphologic development of the clot, which might be considered as the end-result of the processes discussed, was described in detail many years ago. The importance of platelets was recognized in 1882 [*16,17*] but their mechanism of function and adhesive characteristics have more recently been elaborated by Apitz [*18*], M. B. Zucker [*19*], H. Zucker [*20*] and H. P. Wright [*21*]. It now seems clear that the surfaces of platelets are not entirely dependent on their surrounding medium but under certain conditions, such as those encountered postoperatively or with marked infection, the products of platelet activity probably escape through their surface and the cell-plasma interface becomes covered with a film of fibrin. This adhesive surface contact film has such viscosity that even though two adherent particles may have a like electric charge, their mutual repulsion may not suffice to overcome the cementing action of the viscous film. In addition, the hydrophilic colloids which are increased in the blood postoperatively act by reducing the surface charges on the cells, and by modifying the positions of the absorbed water on the cell surfaces. The cells are then enabled to approach each other more closely and, because their electrokinetic potentials are reduced, their surface tension is sufficiently great to overcome their mutual repulsion so that aggregation may take place. Fibrinogen and globulin are potent hydrophilic colloids in this regard and their increase during postoperative periods may be partially responsible for the increase in platelet adhesiveness. Sludging, due to slowing of the blood flow through narrowed channels, makes coagulation easier.

Little understood etiologic factors are known to encourage the coagulation tendency. These include the following: cancer of any tissues but especially cancer of the pancreas, polycythemia vera, familial thrombosing tendency, and individual idiopathic thrombosing tendencies. Once this process is started the thrombus propagates from its fixed adherent head, the body later adhering to the wall of the vessel, often becoming almost a portion of it. A fresh thrombus usually has a loose floating tail which grows and represents a source of potential danger as an embolus.

PREVENTION

It must be admitted that as of this time no means of preventing the development of atherosclerosis in man has been established. This statement is made with full consciousness of the relationship which has been established between the increased occurrence of atherosclerosis and: (a) obesity, (b) hypertension, (c) hypercholesterolemia, (d) diabetes mellitus, and (e) the male sex. The epidemiologic evidence appears to indicate that diets containing saturated fats in proportions of over 30 per cent of the total calories may, over a protracted period, increase the incidence of the thrombosing episodes which are the common terminal episode associated with atherosclerosis. Animal studies confirm this general concept and certainly it appears to be a most promising area for continued analysis.

Recent studies by Ahrens [*22,25*], Bronte-Stuart [*26,27*], and of Malmros [*28–30*] show that the ingestion of corn oil, safflower seed oil and other unsaturated fats with a high content of linoleic acid will reduce the level of the blood cholesterol within a few days or weeks after such a diet is embarked upon. The experience of Malmros with foods which are prepared using corn oil as the source of all fats but which constitute good substitutes for milk, cheese and ice cream is worthy of careful study. Using these foods it has been possible to reduce the blood cholesterol levels without inducing deprivation symptoms complained of by patients on the low fat, low cholesterol diet commonly prescribed in the United States.

The next common assumption regarding the prevention of atherosclerosis needs further clarification. Can a physician assume that by giving a patient a low fat and low cholesterol diet or by using any other means of lowering the blood cholesterol levels he can produce a trend to reabsorption or even prevent the deposition of additonal cholesterol in the walls of the arteries? The answer, for the present, must be that, although this seems possible or even likely, final proof is lacking. Waldron and Duncan [*31,32*] and Buzina and Keys [*33*] have published work which they believe indicates that ingestion of a meal containing large amounts of fat accelerates the ease of clotting of the blood. If this is true one step in the prevention of thrombosis would be to avoid meals containing any appreciable fat. Unfortunately, certain other workers [*34,35*] have failed to confirm this finding.

Borrero et al. [*36*], working in our laboratory with the silicone tube method introduced by Keys, have found no consistent statistically significant changes after the ingestion of a meal of 1,030 calories of cream, and such changes as did occur could be duplicated in the same patients or in other patients by an isocaloric meal of carbohydrates containing no fat. A battery of tests including the one-stage prothrombin time, prothrombin consumption, heparin tolerance, factor V, factor VII, thromboplastin regeneration and others failed to show any changes after such meals. This point is therefore doubtful or at least unsettled at present. It is, of course, possible that new technics may reveal subtle changes in the clotting mechanism after fat ingestion, but the present methods are too crude for this purpose. In the care of patients we must therefore concentrate on those preventive measures which have been shown to decrease the risk of thromboses.

It is now fairly widely accepted that early activity and ambulation after an operation will reduce the risk of thrombosis. The patient should move about in bed very frequently and start ambulation as soon as he is physically able, after some operations on the same day. Stagnation of the blood invites sludging and easy clotting. Evidence has also been presented that compressing the legs with rubber web bandages or stockings further reduces the risk. For enforced and prolonged bed rest the use of an oscillating bed will help to encourage the frequent movement of blood through stagnant channels.

The prophylactic use of anticoagulants during the postoperative and postpartum periods has not been given the attention it deserves. Numerous reports have appeared which have shown a marked reduction in thromboembolism following such therapy [*37–40*]. While most of the preventable thromboses occurring during these periods are venous in location, arterial thromboses are not unusual and may occur in the coronary or cerebral arteries as well as those in the extremities. Storm, Astrup and their coworkers in Copenhagen [*41,42*] have carried this a step further by administering dicumarol before even serious operative procedures such as heart and lung surgery and aortic grafts. The patients are operated upon with prothrombin levels of twenty-two to twenty-five seconds (controls of 15 $\pm$ 1 second). Their basis for this approach is that many clots form during the immediate postoperative period and that prophylaxis later is often incomplete. They have demonstrated that with good surgery, especially in regard to hemostasis, this program can be used without undue risk of hemorrhage and they believe that the risk of thromboembolism is markedly reduced. Several surgeons in the United States are now running test series with similar cases.

For the present, we prepare patients for mitral commissurotomy with anticoagulant therapy especially if their hearts are in atrial fibrillation or if they have suffered from emboli. We lower the prothrombin time to under twenty seconds (control 15 $\pm$ 1 second) for the procedure and raise the level to about twenty-five seconds during the postoperative course. For other surgery the prophylactic use of anticoagulant therapy beginning the second day should be considered unless there are contraindications. If the patient

has never exhibited thrombotic tendencies, seven to fourteen days of prophylactic anticoagulant therapy are usually sufficient to reduce the risk of thromboembolism to the minimum. If he has suffered thromboembolic complications in the past more prolonged prophylaxis may be warranted.

In the present state of our knowledge it is not possible to predict which patients will suffer from a thrombosis. However, there is evidence in our own experience [*43–45*] and in that of others [*46,47*] that once a person has suffered two or more thrombotic episodes anywhere in the arterial system, whether they be cerebral, coronary or peripheral, he is more than ordinarily susceptible to additional similar episodes. This is also true of venous thromboses but they are not within the scope of this discussion.

Individuals may exhibit a tendency toward thrombosis early in life. It is often difficult to determine any abnormality in their clotting mechanism by means of available tests. In a few such patients the prothrombin time, the heparin tolerance test or some index of coagulation may demonstrate some persistent tendency toward easy clotting. We have encountered several families with strong thrombosing tendencies and have previously reported one family in which in three generations eight members suffered sixteen thromboembolic episodes and five of these patients died of such complications [*1*]. This should prove to be a fertile field for genetic studies. It appears quite probable that many of the individuals who exhibit this tendency to easy thrombosis could, with more complete family study, be shown to have an inherited recessive trait. Studies of hemorrhagic traits are revealing new susceptible groups, but such studies are lacking for those showing the thrombosing susceptibility. These groups should be clearly separated from patients with polycythemia vera in whom both hemorrhagic and thrombotic complications develop but who most frequently die of the latter. Prophylaxis in this latter group is difficult because of the paradoxic risk, but long term anticoagulant therapy has apparently reduced the risk of recurrent thromboembolism in some such patients showing this tendency.

There are some patients who "break through" anticoagulant therapy even at optimal levels, with the development of thromboses. This should be regarded as a strong indication for a search for malignancy. The commonest site of the primary malignant lesion is in the pancreas or liver but malignancy anywhere in the body may be responsible. We have seen more than sixty such patients.

The risk is reduced by anticoagulants even when the basic defect is atherosclerosis. There is no evidence that they affect the atherosclerotic impingement upon the lumen or prevent complete closure on this basis. In a large proportion of arterial occlusions the final mechanism is the development of a clot and this can frequently be prevented or delayed. Therefore, long term anticoagulant therapy is indicated as a preventive measure for patients with a history of multiple thrombosing episodes unless there are some specific contraindications.

The details of the use of heparin, the coumarins and the indanedione derivatives have been reported in the literature and will not be dealt with here. Heparin acts to block the development of thrombosis at several levels, including the development of thromboplastin from platelets and the development of thrombin from thromboplastin, prothrombin and calcium, but most completely in the interruption of the conversion of fibrinogen to fibrin. The most important action of the coumarins and indanediones is interruption of the production of factor VII and prothrombin. The former action appears to be most significant. Factor VII influences the one-stage prothrombin test to a greater degree than prothrombin itself. It appears sounder to use a thromboplastin prepared solely from lung tissue for prothrombin determinations since brain tissue which contains factor VII or a similar material may influence the results.

The prevention of the thromboses associated with thromboangiitis obliterans can be summed up in two words, eliminate tobacco. Although this has been clear to those who have worked intensively with this disease for twenty-five years or more, many physicians have been slow to accept this as a fact and have failed to be firm with patients regarding this matter. Countless useless sympathectomies have been performed and have proved to be failures because the patient has continued to smoke. Cessation of smoking almost invariably produces cessation of progress of the disease within three months. The renewal of chewing or smoking will reactivate the disease no matter what type of tobacco is used, be it pipe or cigar, or standard, filtered or so-called denicotinized cigarettes. There can be no compromise in this regard.

TREATMENT

When a patient presents himself for treatment of occlusion of a peripheral artery a number of questions must be answered before a regimen is embarked upon. Some of these may be listed as follows: (1) Is the occlusion due to an embolus arising from a mother thrombus in the heart or great vessels which also requires treatment? (2) How long has the occlusion been present? (3) Is spasm an important contributing factor to the total circulatory deficit? (4) Is the artery involved large enough to justify a surgical approach? (5) Is the segment in an area in which good collateral circulation is apt to be available? (6) Is external pressure playing an important role, as with tumors, a cervical rib or other shoulder girdle syndromes, and if so can this pressure be surgically removed? (7) Are other underlying diseases playing an important role such as diabetes, polycythemia vera or heart disease especially with auricular fibrillation?

The age, general condition of the patient and other questions will arise in specific instances. Once these have been analyzed the treatment should proceed on a clinical but physiologically sound basis. The following material represents the conclusions based on the clinical experience and experimental studies in some thousands of patients over a period of more than twenty-five years. The bibliography supporting these conclusions from our own laboratory and others is too extensive to be included here [*48*].

SURGERY

If the occlusion is acute a decision regarding surgery should be made promptly. Embolectomy from the aorta, iliac, femoral or subclavian-axillary arteries may be successful if performed within four to six hours, but the rate of success decreases rapidly with each succeeding hour. A thrombectomy may also be achieved although this is more difficult because of the diseased intima which, however, may be reamed out with considerable chance of success, especially if this is followed by heparin and oral anticoagulant therapy. Smaller vessels than those mentioned are rarely attacked surgically because of the poor chance of success. Slowly developing progressive obliteration is less amenable to surgery if many segments of an artery are involved. If, however, a single area, e.g. the distal end of the aorta or a portion of an iliac artery is closed, surgery in the form of a homograft or synthetic prosthesis may often be successful. The use of sympathectomy is of doubtful value when the objective is to improve the circulation to the deep tissue since this procedure acts primarily to dilate the superficial vessels. However, when the block involves small peripheral vessels, such as those of the digits, it may prove to be of value. With these general comments regarding the surgical approach, conservative measures will be outlined. The details of the surgical problems will be discussed elsewhere in this symposium.

THE PHYSIOLOGIC USE OF REST AND GRAVITY

With the advent of an arterial occlusion which deprives a limb of a considerable proportion of its blood flow and hence its nutrition, two primary principles should be adopted. The limb should be kept at a sufficient degree of rest to avoid increasing a relative deficit in tissue nutrition by demands for blood above the absolute minimum. Second, the limb should rest at a level about six inches below the heart level in order to encourage easy flow into it and at the same time to avoid the development of edema commonly seen as a result of prolonged total dependency. It is discouraging to find physicians today who still elevate such feet especially in the presence of an open lesion. This archaic practice should be abandoned. The use of an oscillating bed is preferable when available but this should be carefully adjusted so that the foot is elevated just long enough to have a slight pallor develop and depressed long enough to have a moderate rubor appear. This is most commonly achieved by setting the mechanism to elevate the foot of the bed a maximum of six inches above the horizontal and to depress the foot a maximum of ten to twelve inches in each cycle. Foley [*49*] has recently reemphasized the fact that complete and prolonged rest of a limb has certain disadvantages, such as the development of disuse atrophy, decalcification of the bones, and weakness and relaxation of the feet, all of which may make rehabilitation more painful and difficult. Furthermore, exercise itself encourages increased blood flow and activation of the collateral vessels. Therefore we do encourage some weightbearing, first by standing on one foot, then the other. Graduated walking exercises are recommended, even in the presence of ulcers in the feet or small gangrenous areas such as a single digit, except when there is evidence of considerable infection. This represents some change from our

past recommendation of prolonged complete rest for such patients.

VASOCONSTRICTION VERSUS VASODILATION

As a general principle *vasoconstriction should be avoided and vasodilation should be encouraged.*

Vasoconstriction is most commonly caused by: (1) Pain with reflex constriction extending up the involved vessel or neighboring vessels which might otherwise supply the same area. This should be controlled with analgesics if possible, although guarding against addiction is important and often difficult in chronic cases.

(2) Fright, anxiety and nervous tension, so often associated with the occlusion and fear of amputation. This may be combatted with active reassurance by the physician and by the selective use of sedative and tranquilizing drugs. It is also important that the family be instructed on the use of a positive psychology. Nothing is more frightful than the sight of a family ringing the bedside with lugubrious faces.

(3) Tobacco. As already mentioned, this must be prohibited if maximum results are to be obtained. The evidence on this point is now conclusive [*48,50,51*].

(4) Cold. Chilling of the limb should be avoided, whether it be due to draughts or wet dressings. Cold should be used only if the limb is to be amputated. Then an ice pack is often of advantage to localize infection, reduce fever and to afford time to control diabetes or to improve the patient's general condition.

(5) The use of vasoconstricting drugs such as adrenalin,® ephedrin and ergot preparations should be avoided in patients with occlusive arterial disease.

Vasodilation is encouraged by: (1) A warm environment with adequate covers and oversized wool socks.

(2) Reflex heat applied to the abdomen or lumbar area. The application of heat, as for example by the use of hot water bags, infra-red or diathermy, to the distal pregangrenous or threatened distal end of an extremity is contraindicated because it increases the metabolic demands and hence the relative circulatory deficit. Gangrene is frequently hastened or produced in this manner.

(3) Sympathetic ganglion blocks or sympathectomy. While primarily of value for superficial dilation they do have the advantage of affecting only the limb involved as compared with generalized vasodilation.

(4) Typhoid vaccine given intravenously in doses to produce 2° to 3°c. of fever without a chill will also dilate the vessels of the skin without increasing the circulation to the deep muscles. For this purpose we use vaccine diluted to a strength of 100 million organisms per cc., giving five million organisms as a first dose and increasing as necessary to produce the desired reaction. This should be given about twice a week. It is especially helpful in the relief of pain and in the healing of lesions of thromboangiitis obliterans.

(5) Generalized vasodilators, such as alcohol, nicotinic acid derivatives, hexamethonium compounds, priscoline,® regitine,® tetraethyl ammonium halides, ilidar® and arliden have one common disadvantage when used to treat a vascular occlusion of a single artery. They increase the minute vessel bed in many normal areas which dilate easily and may thus actually decrease the blood available to the affected area where, because of spasm associated with pain, collateral vessels are more resistant to dilation. They may also open up numerous arteriovenous shunts in the affected limb proximal to the affected area, thereby short circuiting the blood supply. These mechanisms may actually result in a decrease in flow to the affected area. Alcohol does have the advantage of being an excellent analgesic for this type of lesion. Sublingual glyceryl trinitrite in a dose of $\frac{1}{100}$ gr. (0.6 mg.) will usually dilate the arterial tree for fifteen to 120 minutes [*52*]. However, the arterioles do not respond well to this and the temperature of the skin remains unchanged. Further studies should be carried out using a combination of this drug with methods producing dilation of the minute skin vessels. The potential value of this approach has not been sufficiently clarified.

(6) The injection of drugs into the major artery of an affected limb may be of use as an emergency measure provided that the artery, e.g. the femoral, is readily available, patent and functioning. For this purpose papaverine, priscoline, histamine and other drugs have been used. This has the advantage of supplying a maximum concentration of the drug to the affected limb first. For this purpose it is essential that the drug used have a local action, as for example, at the neuromuscular end plates rather than solely a central action. Repetition of injections into the artery over any considerable period of time is often quite painful and carries

with it an increased risk of local thrombosis as a serious complication.

CHRONIC OCCLUSIVE ARTERIAL DISEASE

For chronic atherosclerosis with multiple thrombosing areas the suggestions already outlined should be applied when indicated. If there is no evidence of gangrene it is advisable to have the patient walk to the point of claudication pain many times a day. This will stimulate the development of collateral circulation, tend to prevent osteoporosis and reduce the risk of disuse atrophy. No effort should be made to walk through the pain barrier since that may increase the deficit, with damage to the tissues.

Ulcers and gangrenous areas should receive daily meticulous observation and care. In general, frequent limited débridement is preferable to major surgery unless a digit or a limb is committed to amputation. Such minute care will often provide satisfactory drainage and adequate time for collateral vessels to be activated and for endothelial and epithelial regrowth to develop from the edges and base of the lesion. A very large number of amputations can thus be avoided. Hands or feet with such lesions should be soaked in normal saline solution at 35° to 38°C. (95° to 100°F.) for thirty minutes once or twice a day to encourage free drainage. Hard crusts and eschars should be very gently removed. Strong antiseptics should not be applied to these lesions, in which bacterial invasion is usually of less consequence than the possible impairment of growth of new cells which may be injured by these agents. Mild antibiotic agents such as tetracycline 3 per cent ointment are frequently helpful but should be applied for only a few hours after each soak. Evidence of local skin sensitivity should be watched for.

SUMMARY

The outlook for patients with acute thromboembolic arterial occlusion is always uncertain. However, with the use of the principles herein outlined, the loss of local tissue, limbs and lives may be reduced to a minimum commensurate with the seriousness of the general and local condition of the patient.

In chronic slowly developing occlusive disease, and in acute episodes once the early phase has passed, the outlook is better than commonly believed. The long range prognosis is frequently good.

Time has proved that a sound regimen, a careful physician, and a cooperative patient may achieve a high percentage of satisfactory results.

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Diagnosis and Management of Peripheral Venous Diseases*

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Of all pathologic conditions which affect the peripheral veins, two groups are of outstanding interest, i.e., acute thrombosis of the deep veins of the leg and degenerative processes in the walls and valves of the veins. Only these two groups will be considered here.

THROMBO-EMBOLIC DISEASE

In this section will be discussed the pathologic condition characterized by deep venous thrombosis in one or both of the lower extremities, sometimes followed by pulmonary embolism.

Up to about twenty years ago, thromboembolism was a particularly dreaded complication. It appeared in one of every 100 patients in medical or surgical wards, and 20 to 25 per cent of those who contracted it died of pulmonary embolism. This implies that one patient died of every 400 admitted, or 25 in 10,000. Those who survived generally had to face six weeks' or more immobility in bed. Apart from these facts, little was known about the disease at that time. Both its cause and its site of origin were unknown. The condition was rarely diagnosed, except in advanced cases with phlegmasia alba dolens or massive embolism. No form of effective therapy existed.

The situation today is entirely different. The condition can be diagnosed at a very early stage with simple clinical methods, and powerful therapeutic agents are available, of which at least one is easy to apply. Before this stage could be reached, a period of intense research was necessary. As a result, certain fundamental data on the origin and development of the thrombotic process were discovered and gained almost universal recognition. Although these facts are well established by now, I shall review them briefly since they must constantly be borne in mind when the question of diagnosis arises.

PATHOPHYSIOLOGY OF VENOUS THROMBOSIS

In 95 to 98 per cent of all cases, the primary origin of the process seems to be in the deep venous trunks of the lower leg. A small adherent thrombus is first formed in one of these trunks. With the deposition of red cells and fibrin, the process grows in the direction of the blood stream. This propagated clot may reach the popliteal vein in a day or two. In at least four of five cases it continues to grow upward through the femoral vein. After another day or so, a dark red, eel-like clot is present in this vein; it floats freely in the vessel lumen, its distal end being anchored to the original thrombus in the lower leg. In about 20 per cent of cases this connection breaks and the propagated clot becomes dislodged, is carried upward and obstructs the pulmonary circulation. In the remaining 80 per cent the clot in the femoral vein sooner or later is brought into contact with the wall of the vein and becomes adherent to it.

The vessel wall reacts to this contact by marked irritation, appearing microscopically as a kind of aseptic inflammation. The irritation presently subsides and is followed by a period of organization of the thrombus. Finally, at a considerably later period, the lumen of the vein is re-established by recanalization of the obstructing thrombotic mass, but the structure of this newly formed femoral vein is abnormal. The most important of all the changes is complete loss of all the venous valves.

Most of the aforegoing information has been obtained with the help of phlebography. This roentgenologic method has also served to elucidate the clinical symptoms associated with the various developmental stages of the thrombotic process. As long as the clot floats freely in the vessel lumen, it seems to produce no clinical symptoms. It is only when the clot has reached sufficient size to fill the lumen and becomes adherent to the vessel wall that such symptoms appear. When a venous segment becomes blocked, the blood stream is obliged to find bypasses through smaller veins and this generally impairs the venous circulation. This gives rise to edema. The irritation of the vessel wall has, as its

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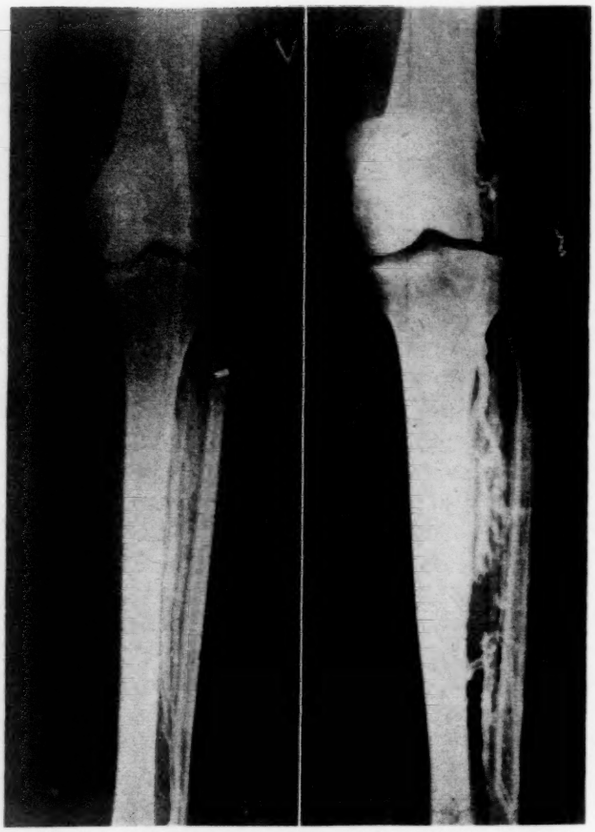


FIG. 1. FIG. 2.

FIG. 1. Normal phlebogram of the deep venous trunks of the lower leg.

FIG. 2. Acute deep venous thrombosis at a very early stage. A filling defect 8 cm. in length is seen in the deep venous trunk.

clinical equivalent, spontaneous pain, tenderness on palpation of the vein and a rise in body temperature. With spreading of the "aseptic inflammation" to the perivenous tissues the sympathetic venous plexuses and those of the associated artery become involved and vasospasm results.

The intensity of the clinical symptoms varies with the site and length of the venous segment which contains adherent thrombotic masses. Thus the very small original thrombus probably always escapes detection. The condition can, however, be diagnosed even when the process is no further advanced than to cause blocking of a few centimeters of a single, deep venous trunk in the lower leg. (Figs. 1 and 2.) The appearance of the affected leg may still be completely normal, but on palpation the incipient edema can be felt as increased firmness of the large muscles of the calf. Marked tenderness is also present on palpation of the venous segment in question, but is lacking both above and below it. On the basis of hundreds of phlebograms, I am firmly convinced that such tenderness practically always is very exactly confined to that part of a deep vein containing an adherent thrombus.

If the thrombotic process is allowed to follow its natural course, the clinical symptoms become increasingly marked. When the process has reached the level of the knee there is intense tenderness over the deep trunks, extending from the Achilles tendon to the knee, and edema is present not only in the muscles but subcutaneously as well. Surface veins may be enlarged as they become involved in the by-passing system. The coincident arteriospasm and venospasm generally give rise to considerable pain, and cause the lower leg to assume a bluish white color.

At an even later stage tenderness is found over the popliteal vein and, still later, over the entire superficial femoral vein as far as the groin. Edema then appears in the thigh as well, and fully developed phlegmasia alba dolens is established.

It must be borne in mind that considerable danger exists in all of the aforegoing stages. Tenderness on palpation is, it is true, confined to that part of the vein in which an adherent thrombus is present. But to this thrombus is not infrequently attached a propagation clot, the extent of which is impossible to estimate since it produces no clinical symptoms whatsoever. Even a thrombus evidenced merely by palpation tenderness over an area a few centimeters in length far down in the lower leg may have an attached clot several feet long, which is liable to break its connection at any moment. This is no doubt why a fatal embolism occurs in so many cases in which no thrombosis of the leg had been diagnosed previously. When a thorough postmortem examination is made in such cases it almost invariably discloses a small matrix thrombus in one of the deep venous trunks of the lower leg. It is, in fact, no exaggeration to state that the patient's life is in imminent danger from the very onset of the process and for several days thereafter, until phlegmasia alba dolens is fully developed.

The necessity for very early diagnosis, so that therapy can be instituted as quickly as possible, is thus apparent. Moreover, it has become increasingly evident that severe post-thrombotic circulatory disturbances arise when a throm-

bosed femoral vein recanalizes, but that this is not the case if the thrombotic process has never extended to the popliteal vein. Early diagnosis of the acute thrombosis enables us to arrest the process while it is still limited to the lower leg, and thus prevent post-thrombotic sequelae.

DIAGNOSIS

With these facts in mind the question arises how, in a large hospital, it is possible to ensure proper and early diagnosis of all fresh cases of thrombosis. First, it must be admitted that, despite much investigation, there is as yet no reliable laboratory test that will disclose imminent thrombosis in some part of the body. Consequently, the only remaining course is to be constantly on the alert for the very first symptoms of the incipient process. Those of the hospital staff who most often are in contact with the patients, i.e., interns and nurses, should be thoroughly familiar with the symptoms for which they must seek.

Among the *general symptoms*, the most important is a rise in pulse and temperature. When, in a patient who has been operated upon, these vital signs follow the normal course and seem to be falling, any fresh rise—even a very small one—after the fourth or fifth day is highly suspicious. This also applies in childbirth if the regular curves show a tendency to rise, and in patients with fractures of the bone. In medical wards it may be more difficult to decide whether or not a rise in pulse and temperature is due to incipient thrombosis but every effort should be made to do so. Another fairly significant sign is a strange and inexplicable feeling of uneasiness or apprehension experienced by the patient. Yet another symptom is that the patient states—sometimes only after questioning—that he has been kept awake for several hours during the night by slight pain or cramp in one calf.

It is also of great importance to note any pulmonary symptoms. The slightest stitch or pain in one side of the chest is highly suspicious of a pulmonary infarction, particularly if the expectorate is even only faintly blood tinged. It can scarcely be doubted that the majority of "pulmonary complications" in newly-operated patients or in others confined to bed are not—as was previously assumed—to be ascribed to bronchopneumonia, but are actually pulmonary infarctions originating from a thrombus which most often is situated in one of the leg veins.

If one or several of these symptoms are present an exhaustive search for the cause must naturally be made. An important part of this investigation is thorough examination of the patient's legs for *local symptoms*. It is not sufficient merely to pass the hands over the legs without lifting the blankets. Complete examination and palpation are necessary. Well-defined symptoms obviously can not be expected in the early stage. The following signs, however, should arouse a suspicion of thrombosis: edema of the lower leg, even if recognized only as increased firmness of the calf muscles, heightened glossiness or tension of the skin and cyanosis even of very slight degree. Even if only one of these symptoms is present, the suspicion of thrombosis is strengthened.

The back of the lower leg should then be palpated. The muscles should be relaxed during examination, the best way of ensuring this is to make the patient bend his knees and keep his feet flat against the lower sheet. If the leg is then palpated from the back, through the muscles of the calf and inward, moving the fingers slowly upward from the Achilles tendon to the back of the knee, the patient may experience definite tenderness to pressure at a certain level. An adherent thrombus must then definitely be suspected, and the suspicion is increased if there is no tenderness when the muscles are pressed together in a sideways movement at this level.

I may seem to have dwelt unduly long on a description of these symptoms but I am firmly convinced that if a combination of several or many of the aforementioned general and local signs are recorded, one can be reasonably certain that early thrombosis is present. It is no longer necessary to rely on phlebography to establish the diagnosis. This method was of great value as long as the whole problem was still in the course of investigation, but it is quite superfluous nowadays. The diagnosis can be made by means of routine clinical methods.

Although thrombosis may occur in practically all patients, it is naturally useful to know the categories in which it is most likely to develop. Judging by a recent investigation at the Mariestad Hospital which, I believe, will be borne out by other investigations of the same kind, the incidence is three times the average in the presence of malignant disease or after major abdominal operations, six times greater when severe anemia is present, and no less than twenty-four times greater after fracture or injury of the lower extremity. As far as age is concerned, the incidence is minimal in children, greater between

twenty and forty years, and rises to three to five times this incidence between forty and seventy years. The most conspicuous predisposing factor, however, is recumbency, irrespective of its cause. This explains why medical patients are even more prone to thrombotic complications than surgical patients.

It would be very valuable if every large hospital were to have a small team of doctors who specialized in thrombosis, one of whom could immediately be consulted in a suspected case to ascertain the diagnosis and to supervise treatment.

THERAPY

Prophylaxis. The most important general prophylactic against thrombosis is, unquestionably, never to keep a patient in bed unless absolutely necessary. Early ambulation after operation, i.e., on the same day or the following one, is now practised in most clinics. Thanks to this precaution alone the incidence of thrombosis has been reduced to at least half the former figure in many surgical departments. The same custom can be applied in maternity departments and could probably be tried, within certain limits, in medical departments as well. In those who are confined to bed, the same attention that is accorded to the fluid balance and intestinal function should, without question, be devoted to the peripheral circulation, which can be encouraged by active and passive movements and by massage.

Prophylactic treatment with anticoagulants, in my opinion, is not to be recommended and does not seem to have many adherents. At a round-table conference in connection with a well planned international congress on thrombosis and embolism held in Basel, Switzerland, in 1954* very few voices were, in fact, raised in support of it.

Anticoagulant Therapy. Nowadays, this form of therapy seems to predominate to such a degree that a report of earlier methods is scarcely called for. Anticoagulant therapy should be instituted as soon as thrombosis has been diagnosed. The primary aim is to arrest immediately any progression of the thrombotic process and, when this has been achieved, to bring about healing. The former goal is best reached by administering a sufficiently large dose of heparin; the very first intravenous injection practically always arrests the process at its initial level. The essential fact in this connection is that the effect of heparin is almost instantaneous, whereas dicumarol and many of its derivatives do not exert their full effect until after twenty-four to forty-eight hours. During this interval the thrombus may progress for a long distance or a pulmonary embolus may become detached. Consequently, treatment of thrombosis should always be initiated by intravenous injection of heparin. This measure was almost unanimously approved at the aforementioned conference in Basel.

The highly important question of the *mode of administration* of heparin also found a tentative solution on the same occasion. General agreement was reached regarding some principles which were, in fact, first introduced in Sweden and have been applied there for a long time. Two alternatives exist for anticoagulant therapy. One is to give heparin alone, and the other to give heparin in combination with dicumarol or its derivatives. On the basis of seventeen years' experience, it appears to me that the *principles of pure heparin therapy* can be formulated as follows.

Using one of the usual brands of heparin, containing 100 international units per mg. of water-free substance, a dose of 150 mg. (3 cc. of a 5 per cent solution) is injected intravenously as soon as thrombosis has been diagnosed. Depending on the time of day at which treatment is started, one or two additional doses of the same size are given. At least four hours should be allowed to elapse between doses, the last one being given late at night. On the subsequent days, three or four injections are given, with early morning and night doses of 150 mg. and an intermediate dose (or doses) of 100 mg. After three to four days the temperature generally has returned to normal, and swelling of the leg and tenderness on palpation have disappeared. Administration of heparin is then decreased to two injections and the patient is allowed out of bed. Treatment is discontinued on the next day and on the following day the patient can usually be discharged from the hospital with an elastic bandage on the affected leg. During the whole time the patient is encouraged to move about freely in bed and is made to perform a series of bending and stretching movements of the leg at intervals throughout the day.

It has been found of the utmost importance for the patient to get up when, or rather before, heparinization is discontinued. Most failures with heparin treatment can, in fact, be ascribed

* Thrombosis and Embolism. 1. International Conference, Basel, 1954. Basel, 1955. Benno Schwabe & Co.

to neglect of this rule. Obviously, this rule is inapplicable in certain cases, for instance when the primary disease necessitates recumbency. In such conditions a form of protracted heparin therapy may be given. Thus, after the acute signs of thrombosis have subsided, a dose of 100 or 150 mg. every evening can be continued for a few days, and then at longer intervals for another week.

In patients in whom phlegmasia alba dolens is already present when they are first seen, heparin therapy should be the same as in early cases. These cases often heal just as quickly, but somewhat larger doses may be required.

When massive pulmonary embolism is the predominating feature treatment should be along the same lines as that already described. During the first twenty-four hours, however, it is advisable to administer heparin (150 mg.) every four hours and also to give the customary antispasmodic agents. It is, in fact, in these cases of embolism that the effect of heparin is most conspicuous. Almost immediately after the first injection the patient is freed from the great feeling of anxiety. Pain and dyspnoea quickly subside and the rapid pulse rate returns almost to normal within a few hours. During the following days these patients can be treated exactly the same as ordinary cases of thrombosis and the total duration of therapy generally is not longer.

When a case of massive embolism is suddenly encountered in the hospital ward, every minute is precious. Treatment must be instituted *immediately;* there must not be the slightest doubt as to the injections to be given. It has been found of value to keep in every ward a printed schedule of action which can be put into operation without delay. An example of such a schedule is given in Table 1.

Heparin therapy according to the principles just described has been used extensively in Sweden. At the Mariestad Hospital, at which a long experience has been accumulated, the mortality rate in heparin-treated cases of thrombosis has been 0.8 per cent. Pulmonary embolism was present in forty-five patients before institution of therapy; all but two recovered. Complications caused by therapy were uncommon. A tendency to bleeding appeared in only about one of every fifty patients and was always of a mild degree.

It may be added that no determinations of the coagulation time were made in the course of routine heparin therapy. It has been shown, in both experimental and clinical investigations, that the coagulation time reaches extremely high levels during the first hours after intravenous injection of heparin, with a fall almost to zero at the end of the four-hour interval between the injections. In our experience these peaks do not appear to constitute any danger to the patient. On the contrary, as shown in a recent study, these peaks are, in fact, the probable cause of the far greater clinical effectiveness of intermittent intravenous injections of heparin than of administration by the intramuscular route, when the coagulation curve never attains these high levels. Although definite evidence is not yet available, it seems possible that the pronounced physicochemical effect of the high concentration of heparin in the blood on the loose, newly formed clots may be the factor which so favorably influences the clinical course.

TABLE 1
SCHEDULE FOR TREATMENT OF PULMONARY EMBOLISM

Time	Intravenous Injections	
	Heparin (mg.)	Papaverine (mg.)
Zero hour (= immediately)	150	80
+1 hour	...	80
+2 hours	150	80
+3 hours	...	80
+6 hours	150	80

NOTE: Subsequently, the same dose of heparin every four hours during the first twenty-four hour period. A few intramuscular injections of papaverine should be added.

However this may be, no determinations of the clotting time were made in our patients. In my opinion, they serve no purpose and are therefore superfluous. As far as I am aware, their omission did not lead to any overdosage of heparin. On the contrary, if heparin is administered according to the scheme described in the aforegoing, there is no reason to fear serious or threatening bleeding.

As far as *combined treatment* is concerned, I have little personal experience. The rules for its application are well known and have been extensively described in the literature. At the conference in Basel most of those present considered that the original dicumarol preparation was still to be preferred, even if the derivatives had

many advocates. The dosage of these drugs is fairly individual and must be adapted to the patient's response. A not inconsiderable number are more or less resistant to the drugs; for this reason it is necessary to make certain that a sufficiently low prothrombin level has been reached before the heparin injections are discontinued. Thus no exact schedule can be set up for administration of these drugs and the therapeutic result is dependent largely on the reliability of the prothrombin determinations.

DEGENERATIVE AFFECTIONS OF THE VENOUS WALLS AND VALVES

The veins of the human body are fairly frail and when attacked by disease, even if of mild degree, they are apt to be so severely damaged that they lose most of their original function. This function is chiefly dependent on the presence of valves, and these particularly fragile structures are the first to be injured by the pathologic process.

The most common venous disease of the lower extremity is valvular incompetence. It is perhaps most often encountered in the form of so-called varicose veins. A surprising fact is that, despite the commonness of this disease, we have little knowledge of its origin and cause. We know that a hereditary factor is much in evidence, and that microscopic examination of an excised venous segment shows mild degenerative changes, generally termed phlebosclerotic. The valves have lost their function either owing to this sclerosis, or secondarily because widening of the vessel lumen prevents them from closing as they did originally.

This disease, which we can conveniently call phlebosclerosis, is of relatively minor importance when it affects superficial veins. The great saphenous vein and its tributaries, and somewhat less often the small saphenous vein, become dilated and tortuous. The patient's symptoms, however, generally are not marked. Unless the varicosity is unusually pronounced there is no edema of the lower leg and only occasionally do ulcers appear. The whole condition is easily controlled by means of ligation, stripping or other conventional surgical methods.

When, on the other hand, phlebosclerosis or some other valve-destroying disease affects the deep venous trunks, this becomes a matter of great importance, since the entire circulation of the leg becomes seriously threatened. To understand the reason it is necessary to review briefly certain facts regarding the normal and pathologic circulation in this limb.

HYDRODYNAMICS OF THE NORMAL CIRCULATION IN THE LEG

The adoption by man of the erect position seems to have had as a consequence a certain tendency to conditional insufficiency of several organs. There is, for instance, insufficiency of the lower part of the back and of the arch of the foot. Most important, however, is a marked disposition to insufficiency of the venous circulation of the lower extremity.

A great help to our present understanding of this circulation are data which have now been assembled that were not available twenty years ago. It appears appropriate to regard the entire vascular system in the lower extremity as *one* system, resembling a U-shaped communicating vessel. The aorta and the large arteries of the leg form one branch of the vessel, the capillaries in the foot and the lowermost part of the leg form the bottom and the large venous trunks and the vena cava form the other branch. In such a vessel, the common hydrostatic laws are valid. The pressure inside the vessel at any given level is always equal to the weight of the column of fluid extending from this point to the upper end of the system, in this case the heart level. Since the U-tube is always completely filled with blood, the result will also be that each time the heart stroke forces a quantity of blood into the arterial branch, the same amount must run out of the upper end, on the venous side, into the heart. In this way the circulation is apparently always maintained, irrespective of the position of the body.

In animals, this rule holds good under all circumstances. In man, on the contrary, a complicating factor is present. In the erect position the intravascular pressure in the bottom of the U-shaped vessel will be very high, owing to the weight of the long column of blood extending from this point to the level of the heart. In fact, in the foot and in the lowermost part of the leg, the intravascular pressure, as found by calculation or actual measurement, is about 120 cm. of water. Its effect on the arteries is practically nil; their walls can resist much higher pressure. The effect on the veins is highly variable and will be discussed later. The effect on the capillaries will first be briefly reviewed.

The osmotic pressure in the capillaries is generally accepted to be approximately 24 mm. Hg

or 34 cm. of water. The intravascular pressure, as already stated, is 120 cm. of water. Even if it is not fully as high as that in the capillaries, it must still be much higher than the osmotic pressure. This can have only one result, namely, filtration of fluid into the interstitial tissues and edema formation.

Even in normal subjects there is, in fact, a certain amount of edema if they stand completely immobile for a few hours. The rate of this formation has been determined in experiments in which normal young persons who had been in the recumbent position, were suddenly made to assume the erect position. It was found that 300 to 400 cc. of edema fluid collected in each lower leg during the first half-hour in the erect position.

It is evident that in healthy persons some mechanism must exist to counteract the general formation of edema in the legs. The most important factor in this respect seems to be the presence of a highly efficient auxiliary pumping mechanism in the lower leg. This pump is constituted by the large calf muscles and by the valves of the superficial femoral vein. When these large muscles contract within their narrow fascial sheath, as in walking, all the blood in the large venous trunks in their midst is forcibly squeezed out of the lower leg—just as one might squeeze the rubber bulb of a blood-pressure manometer—and poured into the femoral vein. When, after a few moments, the muscles relax, this blood cannot flow back down into the lower leg because of the action of the valves in the femoral vein. As a result, the trunks in the lower leg are nearly empty for a brief period and have comparatively low pressure. Consequently, blood is immediately aspirated into them from the small veins of muscles and other tissues, and the pressure in the capillaries is momentarily much diminished. In this way, when contraction follows contraction, the intravascular pressure in the lower leg is constantly maintained at a level low enough to prevent edema formation.

We have here, in fact, a *peripheral heart*, greatly resembling the real one in its general construction and action. The mechanism is highly effective. It has been found that a single muscular contraction squeezes out 70 to 80 cc. of blood, and that repeated contractions lower the pressure in the small veins to about one-third of the initial value. The power of a single one of these "heart strokes" has proved sufficient to overcome the resistance to the outgoing blood stream offered by application to the upper leg of a pneumatic cuff inflated to a pressure above 200 mm. Hg.

It can scarcely be questioned that the action of this "peripheral heart" is mainly responsible for the fact that normal individuals never have any edema of the legs, provided that they move about a little and do not stand absolutely still. A prerequisite, obviously, is that the peripheral heart be completely healthy.

What happens if the "peripheral heart" is attacked by disease of some kind? Just as in the real heart, the *muscles* may be involved, but this rarely occurs and is of little significance in the present connection. The *valves*, on the contrary, often become the site of pathologic changes which impair their function and generally cause them to become incompetent. The effects of this valvular incompetence, as well as its etiology, will be discussed in the following section.

PATHOLOGIC HYDRODYNAMICS IN FEMORAL VALVULAR INCOMPETENCE

On the basis of the foregoing statements regarding the action of the peripheral heart, it is easy to envisage the course of events if the valves, so necessary for the pumping action, become incompetent. The blood which has been squeezed out of the lower leg by the systole-like action of the muscles will then immediately return in diastole, since the valves are unable to prevent it. Consequently, the large venous trunks in the lower leg are never empty. There will be no aspiratory action and, therefore, no lowering of the blood pressure in the small tissue veins and capillaries. The pressure will remain at 120 cm. of water as long as the patient is in the erect position. The inevitable result is the formation of edema. If this edema slowly accumulates it will, after a varying period, cause severe damage to all the tissues of the lower leg, the muscles, skin and ankle joint. Indurative changes will occur, resulting in decreased mobility of the joint and stiffening of the muscles which, in turn, further impair the action of the muscle pump. The arterial blood flow to the skin will be occluded. The normal flow of venous blood from the skin into the deep vascular system will be prevented and the communicating veins may even become dilated and devoid of valves so that a retrograde flow takes place. The circulatory conditions of the skin in the most distal part of the lower leg may then be impaired to such a degree that ulceration and necrosis finally appear. In fact,

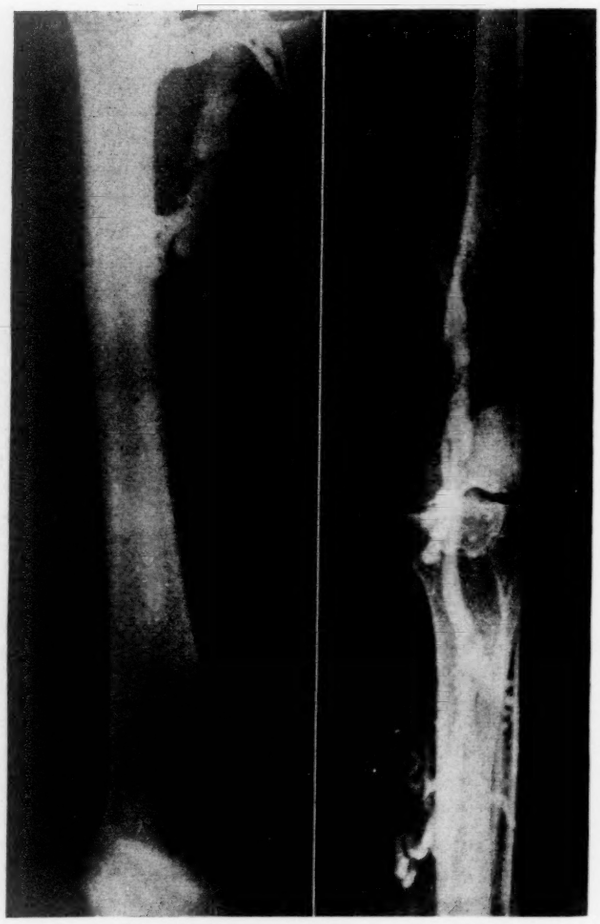


FIG. 3. FIG. 4.

FIG. 3. Retrograde femoral phlebography. Normal subject. The contrast medium is arrested at the uppermost valve.

FIG. 4. Retrograde femoral phlebography. The contrast medium flows downward, past absent valves, into the lower leg.

a syndrome will be produced of which the features have been only too familiar for many years. The fact that this syndrome is, as a rule, not caused by varicose veins but instead almost invariably by femoral valvular incompetence has only recently won general recognition.

ETIOLOGY OF FEMORAL VALVULAR INCOMPETENCE

As is the case in superficial varicose veins, the disease known as phlebosclerosis may also involve the deep venous trunks. This fact, borne out by investigations at the Mariestad Hospital and corroborated by others, is still not universally accepted. In my opinion, however, this disease is responsible for approximately one-half of all cases of femoral valvular incompetence. In the other half, the etiologic factor is an acute venous thrombosis. As mentioned in the first section of this paper, the final stage of femoral vein thrombosis is recanalization as a stiff-walled channel entirely devoid of valves.

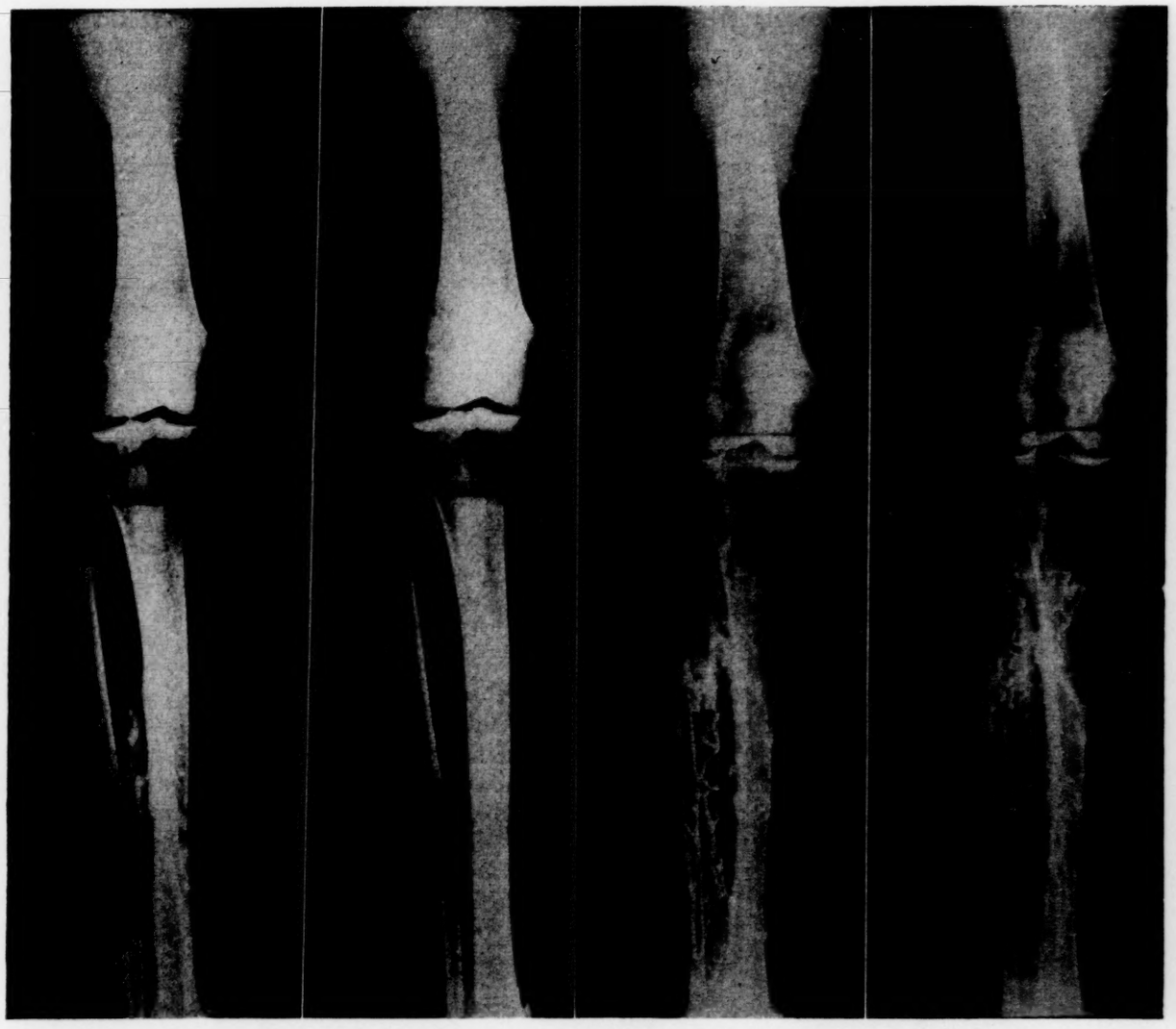
Apart from the etiology, these two groups of cases exhibit almost identical clinical features. In my opinion, this indicates that the presence of valvular incompetence is the element of essential importance. The actual factor underlying this incompetence seems to be of little or no consequence.

DIAGNOSIS

To make an absolutely definite diagnosis of femoral valvular incompetence, phlebography is required. This examination can be made in several ways. If the only object is to establish that the valves are incompetent, the contrast medium can be injected into the upper part of the femoral vein after steps have been taken to ensure that the valves, if any, are closed. I have found that this is best achieved if the injection is made immediately after the patient has suddenly assumed an almost erect position. This maneuver causes the femoral valves to close instantaneously and to remain closed for a short period. The contrast medium, which is heavier than blood, flows downward in the femoral vein but in normal subjects is completely arrested at the uppermost valve. (Fig. 3.) If, on the contrary, the valves are incompetent or non-existent, the dye will flow further downward and will even reach the lower leg. (Fig. 4.) In my experience, if this occurs, it is an unquestionable sign of valvular incompetence. Injection and exposure must, however, be made immediately after the table has been tilted. The leg needs to be in the erect position for only a minute or two before equilibrium is re-established in the U-shaped vessel and blood once more rises in the venous branch. The valves then start to resume their natural open position and contrast medium will trickle downward even through completely healthy valves.

It is, in my opinion, inadvisable to make the examination with the patient recumbent, relying solely on the Valsalva technic to ensure closure of the valves. Moreover, it is not invariably possible to count on the patient's cooperation in this situation.

The main object is not, however, to ascertain the exact state of the femoral valves, but rather the functioning of the peripheral heart. The best way of studying this function presumably is



5A 5B 6A 6B

FIG. 5. Deep venous trunks of the lower leg filled from below. Normal subject. A, immediately after injection of contrast medium. B, trunks empty after three contractions of the calf muscles.

FIG. 6. Same technic as in Figure 5. Femoral valvular incompetence. A, immediately after injection. B, no emptying after three contractions of the calf muscles.

to fill the deep venous trunks of the lower leg with contrast-mixed blood and then to make the peripheral heart beat a few strokes, so to speak. In a normal subject, all the contrast medium is then expelled. If it remains in the lower leg, the peripheral heart is no longer functioning normally.

A simplified technic, often used in the Mariestad Hospital, is the following. The patient is placed in the supine position on a table with its foot tilted 70° downward. He is thus almost in a standing position. The film is placed under the leg. The foot of the patient's sound leg is firmly supported and he is instructed to put all his weight on this leg. The leg to be examined hangs down, completely relaxed, the sole of the foot barely touching a pedal resembling the gas pedal of an automobile. To ensure that the contrast medium enters the deep veins, a piece of rubber tubing is drawn tight just above the ankle.

The contrast medium (20 cc.) is injected into a vein on the dorsum of the foot in the course of about ten seconds. When injection is completed, the first exposure is made. After changing the film the patient is instructed to tramp the pedal

down as far as it will go. The pedal is supported by fairly hard springs and the movement can be accomplished only by strong contraction of the calf muscles. A moment later the patient is instructed to relax the leg completely. He then performs another tramping movement. After

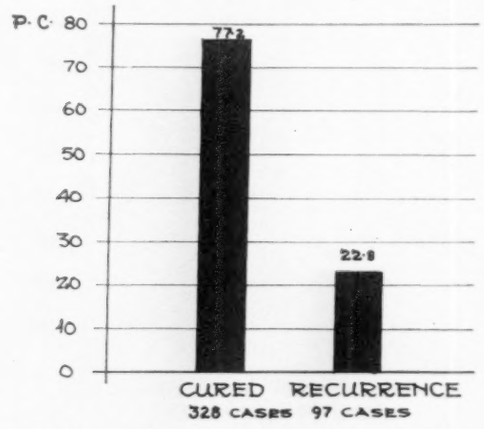


FIG. 7. Three-year results of popliteal vein division. Four hundred and twenty-five ulcer cases.

three such double movements another exposure is made.

Some phlebograms illustrate the information provided by this form of examination. In each figure the picture on the left shows the situation directly after injection of contrast medium, with the leg still relaxed. The picture on the right represents the condition immediately after three powerful contractions of the calf muscles. As seen in Figure 5, in a normal subject the lower leg is completely empty after these movements. An entirely different situation is displayed in Figure 6. The first exposure shows the leg to be nearly engorged with contrast-mixed blood which fills segments of deep trunks as well as veins of muscles, communicating and subcutaneous veins. The three muscular contractions evidently bring not the slightest relief. The right-hand picture shows the leg to be as fully engorged as before. This figure illustrates the complete ineffectiveness of the peripheral heart when the valves are lost. The patient in question had a long history of post-thrombotic sequelae with leg ulcers.

When pathologic features of this nature are encountered, a diagnosis of femoral valvular incompetence is unquestionable.

Recording of the venous pressure during walking, in my opinion, provides little additional information, probably because the pressure is measured in superficial veins only and not in the large deep trunks.

TREATMENT

Conservative treatment of the type described earlier is inadequate for a patient with edema,

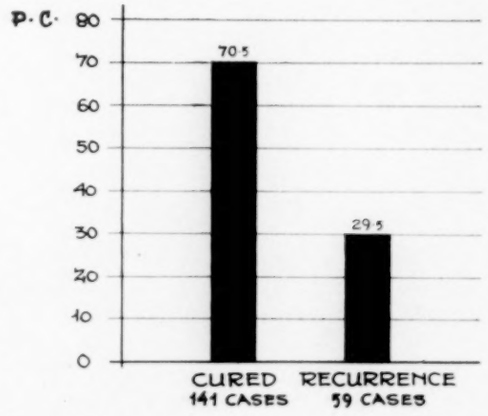


FIG. 8. Six-year results of popliteal vein division. Two hundred ulcer cases.

induration and ulceration of the leg. Moreover, it is fully evident to those who have studied the subject that simple ligation or stripping of a manifestly varicose great saphenous vein also is insufficient. Some additional measure is required that will go more directly to the root of the trouble.

Many surgeons hold the view that a system of communicating veins in the lowest part of the leg, with incompetent valves, is entirely responsible for the skin lesions and ulceration in this region. Consequently, they perform careful dissection and ligation of these communicating vessels.

Another opinion, to which I subscribe, is that all pathologic changes in the lower leg, e.g. muscular sclerosis and atrophy, stiffness of the ankle joint and equino-varus foot, cannot possibly be caused only by incompetence of these communicating veins. They must instead be a direct result of the chronic edema in all parts of the lower leg, for which the femoral valvular incompetence is immediately responsible. On various theoretic grounds, which are beyond the scope of this paper, those holding this view consider that the best way of counteracting the detrimental effect of a valveless femoral vein is to ligate and resect part of this vessel. There are two different points at which this block can be made. Linton introduced ligation of the vein in the groin, just below the entry of

the profunda femoris. For various reasons, I have preferred to do the ligation in the lowest part of the trunk, in the popliteal vein.

Irrespective of the method chosen for the main operation, it is essential to ascertain whether, in addition to the typical syndrome, there is a manifestly incompetent great or small saphenous vein, or incompetence of communicating veins. These are present in a fair proportion of cases and must be dealt with according to current surgical practice.

Furthermore, it is always necessary, in the postoperative period, to make the patient wear some kind of elastic supporting bandage. The length of this period must be determined from case to case.

RESULTS

Sufficient material has not yet been collected to judge which operative method gives the best results. An attempt is now being made to set up a universally adopted classification of the whole material into groups or stages containing cases with the same extent of involvement anatomically, and identical in other respects as well. Leg ulceration is a condition highly prone to recurrence and no definite scheme of treatment can be proposed until large series of three, six, or even nine-year results have been published.

In this paper I shall confine myself to a brief presentation of the results obtained at the Mariestad Hospital with one of the surgical methods, i.e., double ligation and resection of the popliteal vein. More than 750 legs have been treated in this way. We have had no deaths and no serious complications. The results given derive from a series of cases in which, when first seen, open ulceration for an average duration of eight to nine years was present, as well as pitting edema, indurative skin lesions and bursting pain.

Between February 1947 and August 1953, popliteal resection was carried out in 447 such cases. Eleven of these patients died of some other disease in the subsequent years, and in eleven other instances the patient could not be traced. Thus 425 cases, i.e., 95 per cent of the whole series, remained for investigation.

Postoperatively, these 425 patients were kept under continuous observation for *three* years. During this period, 328 (77.2 per cent) remained apparently cured and free from pathologic manifestations. (Fig. 7.) In ninety-seven cases (22.8 per cent) one or more periods of recurrence were noted.

At the time of writing, a group of 200 patients have been kept under the same close observation for *six* years. During this period 141 (70.5 per cent) remained cured. In fifty-nine (29.5 per cent) there was one or more period of recurrence. (Fig. 8.)

To sum up the results, it can be stated that even in ulcer cases of long standing, in which other forms of treatment had been ineffective, popliteal division brought about disappearance of the edema and healing of the ulcers. About three-fourths of the patients remained cured over a period of three, even six years.

Medical Management of Peripheral Ischemic Diseases*

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OCCLUSION of peripheral arteries causing serious ischemia in an extremity may occur suddenly as a result of embolism or rapid thrombosis or gradually as a result of chronic arterial disease such as thromboangiitis obliterans or arteriosclerosis obliterans. Even in the latter, thrombosis often plays a significant role in bringing about the final closure of the artery.

TREATMENT OF ACUTE OCCLUSIVE ARTERIAL DISEASE

Certain manifestations of acute occlusive arterial disease should be considered because they influence treatment. Spasm of unoccluded arteries is a common accompaniment of acute occlusion. Such spasm, which is a major contributing factor to the immediate severe ischemia of the limb, may endure for many minutes or sometimes for hours and may cause severe damage in the endothelium of the arteries distal to the occlusion. Secondary arterial thrombosis may develop in the affected arteries after the spasm relaxes, and in such cases extensive gangrene of the limb almost invariably follows. Considerable damage to the nerve trunks may occur, and even though the circulation may ultimately be restored, ischemic neuropathy may persist. Thrombosis may continue to develop at the site from which an embolus was detached and be a potential source of additional emboli. The thrombus at the site of the occlusion may extend occluding more and more of the collateral anastomosing arteries proximal to the site of the original occlusion. For these reasons, two important principles of treatment of acute arterial occlusion are: (1) relax the arterial spasm as soon as possible, and (2) institute measures promptly to prevent further thrombosis.

Many patients who have sudden arterial occlusion do not receive the best treatment possible. The cold, pale extremity often is elevated and hot water bottles or electric heating pads are applied to warm it. Both of these procedures are inadvisable and may cause serious damage to an already ischemic limb. The extremity should not be elevated because elevation may diminish the flow of blood. Hot water bottles and heating pads should not be used as they may injure the skin. It is better to give no treatment at all than to do something which might injure the extremity or increase the ischemia.

In the medical treatment of sudden arterial occlusion of the extremities the following points are important: (1) Make the diagnosis early. (2) Start proper treatment immediately. (3) Do not elevate the extremity. (4) Do not apply heat locally in any form. (5) Use the Sanders oscillating bed if available in the maximal low-foot and minimal low-head position. If such a bed is not available, elevate the head of the bed 12 to 15 inches. (6) Keep the room temperature between 80° and 90°F. (7) Give ½ gr. (0.032 gm.) of papaverine hydrochloride intravenously or inject 1 gr. (0.065 gm.) of papaverine hydrochloride into the artery proximal to the occlusion. (8) If papaverine hydrochloride is not available or is not effective, give 25 to 50 mg. of tolazoline hydrochloride (priscoline hydrochloride) intravenously or preferably into the artery proximal to the occlusion. (9) Give 1½ fluid ounces (45 cc.) of whiskey every four hours. (10) If treatment is started immediately, anesthetization of appropriate sympathetic nerves by spinal or local anesthesia or paravertebral anesthetization of sympathetic ganglion may be carried out before anticoagulants are administered. (11) Administer anticoagulant agents, preferably heparin and one of the coumarin derivatives.

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Caution should be used in anesthetizing sympathetic nerves while the patient is under the effects of anticoagulants as there is some risk of serious bleeding from these procedures. It is better to avoid blocking the sympathetic nerves if the patient has prothrombin deficiency from dicumarol® or allied drugs or a prolonged coagulation time from heparin. Furthermore, if the other simpler measures for relieving arterial spasm which have already been outlined are not effective, in our experience, temporary sympathectomy will not produce further significant vasodilatation in most cases.

When medical or surgical treatment has made it likely that the extremity will survive, then great care should be taken to avoid any local injury to the extremity which may cause local gangrene and loss of an extremity which apparently has been saved. Administration of dicumarol or heparin should be continued for seven to ten days. If medical treatment is unsuccessful and embolectomy has not been performed, administration of anticoagulants should be discontinued when gangrene is present or inevitable and when amputation seems imminent.

When medical treatment has been started within twelve hours of the onset of the occlusive episode but the circulation does not improve greatly in two to four hours of treatment, embolectomy or thrombectomy may be attempted.

TREATMENT OF PERIPHERAL CHRONIC OCCLUSIVE ARTERIAL DISEASE IN GENERAL

Surgical methods recently devised for dealing with chronic occlusive arterial disease have supplemented but have not replaced the more conventional and less glamorous principles of medical management. This is true for many reasons: Present surgical technics are effective only when the occlusive disease is limited to segments of the larger arteries, and their use does not prevent the development of occlusive disease in other sites. Since many patients with peripheral occlusive arterial disease are in the older age group and have coronary or cerebral arterial disease as well, the hazards of major surgery are high. Finally, reconstructive arterial surgery is of such recent origin that long term follow-up studies to establish its ultimate benefit have not been made as yet.

Since the medical management of a chronically ischemic limb is much the same regardless of the cause for the ischemia, several conditions can be grouped together for the purpose of discussing the treatment. These conditions include arteriosclerosis obliterans, thromboangiitis obliterans (Buerger's disease), the chronic ischemia that results from embolic arterial occlusion in a limb that survives the acute episode, and the rarer types of arterial thrombosis due to polycythemia vera and idiopathic or simple thrombosing disease. Special methods of treatment pertaining to certain of these conditions will be mentioned in the discussion of general principles.

MEASURES TO PREVENT PROGRESS OF THE DISEASE

Abstinence from Tobacco. Tobacco is potentially harmful to all patients who have occlusive arterial disease because it produces constriction of small arteries and arterioles and thereby compromises collateral circulation. In thromboangiitis obliterans, tobacco has an even more specific effect and indeed seems to be implicated in the etiology of this disease, for a non-smoker rarely has thromboangiitis obliterans and, if present, it rarely progresses if the victim abstains from tobacco totally and permanently. Abstinence from tobacco, therefore, is a helpful adjunct to treatment of all types of occlusive arterial disease but is essential in treatment of thromboangiitis obliterans.

Control of Lipemia. A relationship between the metabolism of lipid and atherosclerosis has been established. It is logical, therefore, that an attempt should be made to control lipemia that is so frequently associated with arteriosclerosis obliterans, especially in patients less than sixty years of age. This can be accomplished, although not always consistently and satisfactorily, by limiting the dietary intake of fat to 30 or 40 gm. per day. In our experience lipotropic agents, such as choline, inositol and methionine, have not been satisfactory in reducing blood fats on a long term program. The use of thyroid extract and sitosterols has not produced consistent results. The feminizing effects of estrogens and the inconvenience and expense of administration of heparin have prevented wide acceptance of these as agents to reduce blood fats. Experience with large doses of nicotinic acid and various unsaturated vegetable oils has been encouraging but too limited for adequate evaluation.

Control of Diabetes Mellitus. Approximately 20 per cent of patients who have arteriosclerosis obliterans also have diabetes mellitus. Adequate control of the diabetes is desirable not only

because it may retard atherogenesis but also because it may help to prevent or ameliorate complications such as infection and neuropathy which make the management of arteriosclerosis obliterans more difficult.

Control of Polycythemia. When chronic occlusive arterial disease is associated with or results from polycythemia vera, specific treatment directed at the blood dyscrasia is imperative. Repeated phlebotomies and the administration of radioactive phosphorus are usually the treatment of choice.

Control of Thrombosing Tendencies. Chronic occlusive arterial disease may result when emboli become detached from a mural thrombus within the left side of the heart or when a distinct propensity to thrombosis in normal or diseased arteries occurs. Under such circumstances it is often advisable to administer anticoagulants on a long term basis to inhibit the thrombosing tendency.

Adrenal Corticosteroids. Theoretically the adrenal corticosteroids should be helpful in suppressing the inflammatory lesions of thromboangiitis obliterans. As a matter of practical fact, however, the expense and dangers of long term treatment with these compounds have not been justified by the results obtained.

MEASURES TO INCREASE CIRCULATION

Once major arteries have become occluded, they tend to remain so in spite of any medical treatment presently available. An exception to this is thromboangiitis obliterans in which recanalization of the occluding thrombi occasionally occurs as part of the natural history of the disease.

The objective of medical treatment then is to take maximal advantage of collateral circulation by eliminating arteriospasm and promoting dilatation of collateral channels. The elimination of tobacco is one step in this direction. Other measures include the use of arterial dilating drugs, certain mechanical devices, artificially induced fever, a warm environmental temperature, and interruption of regional sympathetic nerve supply by various means.

Drugs. There are on the market numerous drugs advertised and advocated for use in dilating the peripheral arteries. These include tolazoline hydrochloride (priscoline hydrochloride), nicotinic acid, dibenzyline, hexamethonium, azapetine (ilidar®) and nylidrin hydrochloride (arlidin). Most of these are effective vasodilators for normal persons and in certain arteriospastic conditions, but they are disappointingly ineffective when extensive organic occlusive arterial disease is present. In our experience 1 or 2 ounces of ethyl alcohol, usually given in the form of whiskey before meals and at bedtime, is as good as, and perhaps superior to, any of the peripheral vasodilating drugs presently available. In addition it is an excellent anodyne and sedative and may be helpful in controlling the pain of the ischemic lesions. Unless patients customarily use alcoholic beverages, we recommend their use only for short periods of two to six weeks when ischemia is especially severe or ischemic ulcerations are present. In prescribing alcohol, the physician must always make sure that he is not condoning its use by a chronic alcoholic or that he is not rekindling the thirst of a former chronic alcoholic.

Mechanical Methods. Postural or Buerger's exercises have been advocated as helpful in improving circulation to ischemic extremities. These consist simply of elevating the extremities for two or three minutes and then placing them in a dependent position for a slightly longer period. This can be repeated several times. It is doubtful that such exercises are of sufficient value to warrant their routine use.

The Sanders oscillating bed affords postural exercises to the entire body with no effort on the part of the patient. Hospitalized patients are placed on this bed for eight of twenty-four hours. Peripheral edema, uncontrolled infection and cellulitis are contraindications to the use of the oscillating bed. Only rarely is it advantageous for a patient to purchase an oscillating bed for home use.

Other mechanical devices include the alternating positive and negative pressure boot (Pavex) and an apparatus to produce intermittent venous occlusion. Both have largely been abandoned. The syncardon, introduced in Europe, applies external pressure to the ischemic limb in a peristaltic fashion synchronous with the pulse wave. It has not been adequately tested.

Fever Therapy. Repeated injections of triple typhoid vaccine or other foreign protein have been used to induce fever and thereby promote vasodilatation. A febrile reaction with oral temperatures between 100° and 102°F. is desirable. The dose must be individualized to obtain this result without producing higher temperatures with violent chills which cause exhaustion

and malaise. When triple typhoid vaccine is used, a small initial dose of about 5,000,000 killed organisms is injected intravenously; for later doses the amount is increased as necessary to produce the desired fever. Fever therapy of this type is reserved largely for patients with ischemic lesions due to thromboangiitis obliterans since they are usually in the younger age group and better able to tolerate it than older persons.

Warm Environment. A warm environmental temperature tends to promote vasodilatation while exposure to cold may compromise collateral circulation by a direct and reflex action to cause vasoconstriction. Often blood flow can be stimulated in ischemic feet by placing a thermostatically controlled heating unit over them. Heat can be injurious to ischemic extremities, and hence it should be employed only when there is thermostatic control and the temperature within the box should never exceed 90°F. The feet must be shielded from the source of heat which usually consists of one or more 25 watt electric light bulbs. Heat must never be applied directly to ischemic extremities in the form of hot water bottles or heating pads. The heating box should not be used if it makes the pain worse or for patients who are so confused or delirious that they may injure their feet on the edges of the box.

Regional Sympathetic Denervation. Such denervation has a distinct advantage over use of sympatholytic drugs as it selectively inhibits sympathetic impulses in the ischemic extremity or extremities; whereas, administration of sympatholytic drugs produces a generalized effect. Regional sympathetic inhibition is often helpful in increasing arterial circulation to the skin of ischemic extremities and therefore is indicated whenever ischemia of the skin is extensive and integrity of the skin is jeopardized. It may promote healing of ischemic ulcers and help prevent their recurrence. It is useless in the treatment of irreversible gangrene. Patients subjected to local sympathetic denervation should be cautioned that it merely tends to improve collateral circulation and does not affect the basic disease; therefore, other measures of treatment continue to be important.

For elderly patients, whose general condition might make surgical sympathectomy hazardous, effective chemical sympathectomy can be obtained with minimal risk by expert injection of absolute alcohol around the second or sometimes second and third lumbar paravertebral ganglia. This is usually done with the patient in a prone position and under light anesthesia with thiopental sodium. Roentgenograms assure accurate placement of the needles. Approximately 3 per cent of patients will experience a distressing somatic neuritis for several weeks following the block, presumably due to accidental injection of the alcohol around somatic nerve roots. This technic has achieved adequate sympathectomy as determined by sweating tests for 65 per cent of patients. The sweating defect persists for from six months to more than five years.

RELIEF OF PAIN DUE TO ISCHEMIA

Intermittent Claudication. Intermittent claudication which usually is not described as a severe pain is troublesome only because it occurs when active muscles become temporarily ischemic. Therefore, it limits the distance which a patient can walk and is promptly relieved when the patient stops walking.

Medical treatment of intermittent claudication is not satisfactory. Heparin, testosterone and the gamut of vasodilating drugs have proved to be practicallly worthless when evaluated objectively. Occasionally, a course of injections of deproteinated pancreatic extract (depropanex®) is helpful. Five cubic centimeters are given intramuscularly daily for a week, every other day for two weeks and then twice weekly for an indefinite period if benefit is being obtained. Usually patients can be taught to live with their intermittent claudication and are content to do so if they are reassured about its significance. They learn that they can walk farther if they walk slower. They should be assured that it will do no harm to walk to tolerance as frequently as is desired, and indeed it is probably beneficial to do so. Since ischemia of the skin, not of muscle, leads to irreversible gangrene and amputation, patients with intermittent claudication should be more concerned about the proper care and hygiene of their feet than about the distance they can walk.

In the treatment of intermittent claudication surgical reconstruction of arteries has been most helpful.

Rest Pain. When ischemia of the skin, subcutaneous tissues and nerves becomes profound, it causes pain in the affected extremities during rest. Rest pain of ischemia includes pretrophic pain, pain of ulceration and gangrene, and pain of ischemic neuropathy. These types of pain are

severe, are worse at night and are resistant to narcotics. They prevent sleep, inhibit appetite and wreck morale. The tortured patient begs for relief which frequently can be achieved only by the liberal use of narcotics. When aspirin and codein fail, we prefer the use of levorphanol tartrate (levo-dromoran) in doses of 2 mg. or more given at regular intervals of every four or six hours. Sometimes the administration of chlorpromazine hydrochloride (thorazine®) in doses of 25 mg. every four hours potentiates the effect of levo-dromoran. When this regimen fails, it becomes necessary to use meperidine hydrochloride (demerol®) or morphine.

Persistent severe rest pain of ischemia is an ominous sign for the future survival of the limb, and a patient whose pain is severe enough to require narcotics deserves hospitalization so that measures to increase circulation may be instituted promptly and properly. Rest in bed is essential for such patients, and they must be given enough narcotic so that they are not obliged to allow the ischemic leg to dangle over the edge of the bed in an attempt to get relief from pain. This is a vicious practice, for it favors the accumulation of edema which further embarrasses the circulation to an already impoverished extremity.

Unfortunately, in some cases uncontrollable rest pain is a justifiable indication for amputation, even though irreversible ischemic ulceration or gangrene is not present.

MANAGEMENT OF ULCERATION AND GANGRENE

Prophylaxis. Nothing is more important to patients with chronic occlusive arterial disease than careful and diligent instructions about the proper care and hygiene of ischemic extremities. Physicians familiar with the treatment of occlusive arterial disease often lament that frequently minor injury leads to major amputation. It is estimated that gangrene can be avoided in more than half of the cases in which it leads to loss of a digit or extremity, if proper precautions are exercised. The patient must be ever vigilant to avoid crushing or bruising ischemic hands or feet and to avoid scratches, cuts, fissures in the skin, burns, blisters and frostbite. Only comfortable shoes that do not bind or rub should be worn and new shoes should be broken in gradually by wearing them about an hour daily. Immersion of the feet in hot water, and the direct application of hot water bottles or heating pads to the feet should be strongly condemned. Likewise exposure to cold temperatures can be injurious unless the patient is warmly attired, and the ischemic extremity is adequately protected by proper footwear. Toenails should be cut straight across. Corns, calluses and bunions should not be trimmed or incised. Removal of ingrown toenails is hazardous. Minor surgical procedures on the feet should be avoided. If the skin is excessively dry and tends to crack or scale, hydrous lanolin or cocoa butter should be applied gently every day. Patent medicines for the treatment of corns, calluses and athlete's foot should be avoided, for they contain chemical irritants such as iodine, merthiolate, phenol, cresol, lysol or similar agents which can harm the ischemic skin. Adhesive tape or adhesive plaster should not be applied to the skin of ischemic extremities. Trichophytosis can be treated in the acute stage by soaking the feet for half an hour twice daily in a 1 in 10,000 solution of potassium permanganate. In the subacute stage, trichophytosis can be effectively and safely controlled by the application of an ointment containing undecylenic acid (desenex) to the affected areas at bedtime and the use of a dusting powder containing undecylenic acid in the shoes during the day. When severe ischemia with or without ulceration or gangrene is present, the patient should be confined to bed and gradual increase of ambulation should be permitted only after the skin lesions heal and circulation has improved.

Local Treatment. Conservatism is the wisest course in the local treatment of ischemic ulcers. Overzealous attempts to combat infection and to encourage healing usually result in more necrosis, for ischemic tissue is extremely vulnerable to chemical irritants.

To eradicate infection, the hand or foot may be soaked in a saturated solution of boric acid three or four times daily. At times it is advantageous to use moist packs of a solution of boric acid, but maceration of viable tissue by prolonged application of wet dressings should be avoided. Occasionally a 1 in 10,000 solution of potassium permanganate may be used to soak the foot. The temperature of solutions applied to ischemic lesions should never exceed 95°F.

It is our impression that ointments impede healing and the fear of sensitivity reactions has made us hesitant to use antibiotics and sulfonamide derivatives locally on ischemic lesions. If sensitive organisms are cultured from the

lesions, appropriate antibiotics are administered systemically.

When a necrotic crust or eschar covers an ulcer, enzymatic débridement using wet dressings of streptokinase 100,000 units and streptodornase 25,000 units (varidase®) per 20 cc. of physiologic saline solution may be helpful in removing the crust. Similar quantities of the enzymes may be dissolved in 5 cc. of sterile distilled water and added to a jar of carboxymethyl cellulose jelly which can then be applied to the ulcer. Surgical débridement of ischemic lesions should be avoided if at all possible, but when necessary should be gentle and conservative.

When infection has subsided, the application of dry powdered blood cells to the ulcer often promotes healing. The cells are allowed to form a dry crust over the ulcer, and this crust is removed every three or four days by application of wet dressings of a solution of boric acid. After the base of the ulcer has been inspected and progress noted, more cells are applied.

It is apparent, of course, that the measures to increase circulation discussed previously should be employed in addition to local applications. Diabetes mellitus, if present, should be strictly controlled.

Refrigeration. When amputation is inevitable but the general condition of the patient makes surgery hazardous, valuable time can be gained, pain can be relieved, and absorption of toxins stopped by packing the ischemic extremity in ice. This can be continued for several days or weeks if necessary while the patient is being prepared for amputation. Refrigeration is contraindicated, however, as long as there is hope for saving the limb. Amputation should be performed well above the level of refrigeration to avoid delayed healing.

Amputation. A detailed consideration of amputation is beyond the scope of this discussion of medical management, for indeed, amputation is the end result of failure of medical management. Nevertheless it is pertinent to note that particularly in thromboangiitis obliterans, amputations of digits or transmetatarsal amputations have a reasonable chance for success if pain and infection can be controlled and the procedure is deferred until maximal benefits have been obtained from conservative treatment.

COMMENT

All patients having chronic occlusive arterial disease deserve an explanation of their condition and meticulous instructions about the care of ischemic extremities. In addition, all patients with thromboangiitis obliterans and most patients with arteriosclerosis obliterans should be strongly, emphatically and unequivocally advised to abstain totally and permanently from the use of tobacco in any form. Otherwise the treatment of chronic occlusive arterial disease can be individualized to a considerable degree. When ischemia threatens the integrity of the skin or when ischemic lesions are already present, hospitalization is advisable for treatment as outlined previously. However, many patients who have peripheral occlusive arterial disease have relatively minor ischemia and no symptoms except intermittent claudication which is seldom incapacitating. For such patients the value of drug therapy or mechanical devices to improve circulation is certainly open to question. These are the patients who frequently receive too much medicine and too little explanation and advice.

The treatment of chronic occlusive arterial disease leaves much to be desired, for actually the ischemic complications and not the basic disease are being treated symptomatically. Furthermore, the treatment is likely to remain unsatisfactory until we gain fundamental knowledge concerning the cause and pathogenesis of arteriosclerosis, thromboangiitis and thrombosing tendencies.

Surgical Management of Peripheral Ischemic Disorders*

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In recent years considerable advances have been made in the surgical management of peripheral ischemic disorders and a better understanding of the results of older methods has been achieved. It is not the purpose of this communication to attempt to evaluate these methods from a review of the literature but rather to record impressions gained largely from personal experiences. It will be concerned principally with the possibilities of restoring blood flow through, or about, obstructed main arterial pathways. The value of sympathetic denervation in the vasospastic and obliterative diseases will be dealt with more briefly.

THE VASOSPASTIC DISORDERS

Large experiences with arterial circulatory disorders which are primarily vasospastic in nature have resulted in convincing evidence that surgical sympathetic denervation is of real benefit. If annoying or disabling symptoms are present or if the disease is progressive, and if advice as to maintenance of body warmth and the use of general vasodilating agents does not afford relief, sympathectomy is in order. In my experience autonomic blocking agents and other vasodilators have not proved effectual except in the mildest cases. In the common ill-defined vasospactic disorders an excellent result is practically always obtained from sympathectomy. The same is true with regard to specific vasospastic syndromes such as acrocyanosis and vasospasm associated with livedo reticularis. In those patients who have vasoconstrictive sequellae after cold injury these complaints are always minimized and cold sensitivity is reduced. In certain cases, however, some sensitivity to cold persists. Ulcers remaining as the result of superficial or limited deep gangrene generally heal promptly. The pain on weight bearing, however, which so often follows trench foot and which apparently is due to somatic nerve injury is rarely affected, even when intense vasospasm has been present and has been abolished by the procedure. In idiopathic Raynaud's disease the results are variable. In general, they are better in those cases not associated with far advanced changes or scleraderma. Attacks consequent to emotional excitation are always eliminated. Attacks precipitated by exposure to cold, with the rarest exceptions, either cease or occur with less frequency and intensity. The results appear to be lasting in the lower extremities and this is usually the case with regard to the upper extremities. In some instances, however, symptoms recur in the upper extremities together with evidence of apparent return of sympathetic activity. Such apparent return of sympathetic activity, peculiarly enough, is observed more often in cases of Raynaud's disease than in any other vascular disorder for which upper dorsal sympathectomy is performed. Although opinions differ widely, it is my belief that such disappointing long term results are noted less frequently after the Smithwick type of preganglionic sympathetic denervation and root section than after other types of sympathectomy.

NON-SPECIFIC OBLITERATIVE ARTERITIS

Those cases of obliterative disease affecting principally small arteries and associated with symptoms somewhat like those of idiopathic Raynaud's disease constitute an especial challenge. Their true nature is poorly understood. The affected vessels show evidence only of a non-specific obliterative arteritis. The disease is not infrequently progressive. In my experience it generally has not responded to steroid or other medical therapy. It has uniformly been benefited

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by surgical sympathetic denervation. In some instances the good result appears to be lasting. In others, unfortunately, the disease progresses and the initial benefit is lost. For this reason it seems wise to utilize operative treatment with the full realization that the result may be compromised by extension of the disease process.

REFLEX DISTURBANCES

True major causalgia may or may not be associated with vasoconstriction. At times the vasoconstriction is extreme and the hand or foot is markedly ischemic. Regardless, however, of the presence or absence of vasospasm the response to treatment is the same. Occasionally the agonizing pain is relieved entirely by one or more sympathetic procaine blocks. If sympathetic block brings about relief only for the duration of the anesthesia, or if successive blocks fail to result in progressively longer periods of relief, they should be abandoned and operative denervation carried out without further delay. Operative sympathectomy always results in brilliant alleviation of symptoms. This is not true in the so-called minor causalgias or post-traumatic reflex disturbances. They, too, may or may not be associated with vasospasm, and with them also therapy brings about similar results with regard to pain regardless of the presence or absence or intensity of the vasoconstriction. Vasospastic phenomena, of course, are always abolished by sympathectomy. In one type of this disturbance, that accompanying the postphlebitic state and characterized by severe pain and hypersensitivity to touch, complete relief has never in my experience followed sympathetic blocks alone and has invariably followed operative sympathectomy. On the other hand, in the more common sort which is a sequel to trauma, operative manipulation or arthritis, sympathectomy yields variable results. In some instances, sympathetic denervation results in permanent benefit. All too often, however, this is not the case and, in spite of alleviation of any existing vasospastic complaints, the pain continues. Peculiarly enough, this is not infrequently true in patients who have experienced complete or nearly complete temporary relief from one or more procaine sympathetic blocks. This extraordinary sequence of events is difficult to understand except by the assumption that psychogenic factors play an important role in the symptomatology of this disorder and that they are unfavorably influenced by the finality with which operative therapy is so commonly regarded. In contrast, particularly in cases which have not been long neglected, cures can be obtained by reassurance, insistence upon active use of the affected part, control of any edema present with elastic compression support and the use, when needed, of sympathetic blocks or autonomic blocking agents. For this reason one should resort to operative sympathectomy in this disorder only with the greatest reluctance and then without promise of relief.

TRAUMATIC INTERRUPTION OF MAIN ARTERIAL PATHWAYS

Concepts concerning the surgical management of wounds of major arteries have undergone a radical change in recent years. The importance of arresting hemorrhage, replacing blood loss, and the necessity for early careful débridement of all devitalized tissue has long been recognized. Not many years ago, however, the wounded vessel was generally treated by ligation or ligation and division in case of incomplete severance. Resultant ischemia was managed by proper posturing of the part, sympathetic blocks, sympathectomy and other adjuvants. In instances in which no ischemia of the extremity was present and in which there was no necessity for débridement, surgery was considered inadvisable as initial treatment. Not a few such patients had to be treated later for aneurysm or arteriovenous fistula. Now it is recognized that direct repair of the injured artery is the ideal treatment and should be employed whenever proper facilities and personnel are available. This can be accomplished according to the type and extent of injury by lateral suture, end-to-end suture, or by the insertion of a graft. Success means restoration of good circulation and the avoidance of aneurysm or arteriovenous fistula. That such a direct approach can be made successfully is evident not only from limited civilian experiences but from those made during the Korean conflict as well. The chief limiting factor has been the time interval between injury and repair. Time is of importance principally because with increasing delay there is more likelihood of thrombosis of the distal arterial tree. The successful re-introduction of the retrograde flushing procedure as an adjuvant in treating cases of arterial embolism offers promise of overcoming the problem of distal arterial thrombosis. If one cannot extract the clot by aspiration through the open artery, one can often wash the

clot out by retrograde perfusion through a small distal artery such as the posterior tibial.

ACUTE ARTERIAL EMBOLISM AND THROMBOSIS

In no other condition are the dire consequences of sudden interruption of blood flow through an important arterial pathway and the dramatic return to a normal state with restoration of blood flow so evident as in cases of acute arterial embolism to major arteries. It seems clear to me that all patients with acute arterial embolism associated with ischemia should be treated by embolectomy as soon as is possible with the exception of those who are so ill that survival seems out of the question. There is little profit in attempting to evaluate the result of direct arterial surgery by comparing a series of patients so treated with another series treated medically. The two groups are of necessity not comparable. The first group includes patients with an imminent threat of gangrene and in rare instances patients who have survived an embolism for some time and present a markedly ischemic extremity with rest pain, anesthesia, etc. The latter group includes patients who arrive for treatment late with well established gangrene, those who have undergone prompt spontaneous improvement of circulation of such a degree as to make it evident that the limb has an excellent chance for survival under any circumstances, and a small number who are considered moribund at the time of the embolism. In my own institution the mortality has been slightly, but probably not significantly, lower in those who have been treated by direct arterial surgery than in those who have not been so treated. In the latter group approximately half the patients have been admitted with well established gangrene and amputation has been necessary. In approximately one-fourth there has been a spontaneous quick return of adequate circulation and the results have been reasonably satisfactory. Another quarter of them includes a few patients who have been moribund at the time of embolism and have died, and a small number who have been treated for impaired circulation some time after embolism by sympathectomy with good results. In this group only one-third of the patients have survived with adequate circulation in the affected extremity. In the larger group treated by direct arterial surgery approximately 70 per cent have survived with adequate circulation, and good circulation has been restored to the affected extremity in over 80 per cent of all the patients including those who have lived and those who have died. Both the survival rate and the likelihood of successful restoration of circulation are related to the underlying disease. The mortality is only about 5 per cent in cases of rheumatic heart disease and considerably higher in instances of arteriosclerotic or hypertensive cardiovascular disease, myocardial infarction, etc. The mortality is not related to the location of the embolism. Restoration of adequate circulation is achieved in over 90 per cent of the patients with rheumatic heart disease and in approximately 70 per cent of those whose embolism is on a different basis. The difference in outcome is undoubtedly related to the younger age group of those with rheumatic fever and to their greater freedom from peripheral arteriosclerotic disease.

Several erroneous concepts have arisen. One is a false sense of optimism concerning the outcome in cases of embolism to the main arteries of the upper extremity. My experience and that of my associates does not justify such optimism. In this institution during a seven and a half year period there were six cases of brachial, axillary and subclavian embolism not treated by embolectomy. Amputation was required in four of the six patients. Another relates to the time interval after embolism during which one has a reasonable chance of success. The policy has often been adopted that embolectomy is not justified after the passage of six, eight, ten or twelve hours. Setting up of such rigid time restrictions is unjustified. There is no doubt that early embolectomy should be the cardinal principle of treatment and that early embolectomy is attended by a very high percentage of surviving limbs. Adequate circulation has been restored in 96 per cent of the extremities treated in less than six hours as well as in 85 per cent of those treated within thirteen hours after the onset of embolism. The situation, however, is certainly far from hopeless in those patients in whom direct arterial surgery is carried out later. Adequate circulation was restored in 67 per cent of the patients who were treated from thirteen to twenty-four hours after embolism and in precisely the same percentage in a small group treated from forty-five to forty-eight hours after embolism. Three-quarters of the few patients who have been treated for markedly ischemic extremities some days or weeks after embolism have had restoration of good circulation. In these exceptional cases it is sometimes preferable to bypass the

obstruction with a grafting procedure rather than to perform an embolectomy. The earlier treatment is carried out the better are the results of embolectomy because as time passes the likelihood of thrombosis occurring in the arterial tree beyond the site of the embolus increases. Adequate circulation has been restored in all our patients who had no distal thrombosis and in only 55 per cent of those in whom distal thrombosis was encountered. Now that the retrograde flushing technic has been established as a valuable adjuvant it is certain that the rate of success will be considerably better in those in whom embolectomy is carried out after propagated thrombosis has occurred. One group in which even this technic is almost sure to fail is that in which there is extensive thrombosis beyond the embolus together with severe arteriosclerotic changes in the arteries themselves. Such a combination of circumstances and delay to the point where permanent ischemic damage has been taken place seem to be the only limiting factors with regard to restoration of circulation in these cases.

Sudden arterial thrombosis occurring in patients with localized or diffuse arteriosclerosis presents a similar but more difficult problem. Experiences with efforts to restore circulation through or about the obstructed segment are relatively few. They are, however, somewhat encouraging. If the occluded portion is segmental there is a reasonable chance of success from immediate thrombectomy and thromboendarterectomy or a bypass grafting procedure. The chances are poorer when extensive thrombosis has occurred distal to the point of the initial thrombus formation. In a few cases of this sort it is possible to remove the thrombus by arteriotomy and retrograde flushing. When blood flow cannot be restored through the main artery, sympathectomy is occasionally of dramatic aid.

OBLITERATIVE ARTERIAL DISEASE

Until the advent of restorative surgery for obliterative arterial disease the only surgical procedure which could be utilized with expectation of improvement in circulation was sympathectomy. There can be no doubt that sympathectomy is a useful measure in many instances. Frequently it brings about a dramatic change for the better. A cold foot may become warm. Good venous filling often ensues. Hypesthesia may disappear. Rest pain not infrequently subsides completely or is ameliorated to the extent that with proper posture it becomes tolerable and may gradually disappear. Superficial ulcerations may heal. Abnormal sweating, if present, is abolished. Sympathectomy, however, has definite limitations. In some instances the obliterative process is so extensive and the element of vasoconstriction so small that little change for the better takes place. When this operation is carried out more or less as a last resort trial procedure before deciding to amputate because of ischemic necrosis of the digits, the percentage of salvage of limbs is low. Perhaps its chief limitation, however, is its general lack of significant improvement in the alleviation of intermittent claudication. Even though they may be relieved of coldness, hypesthesia and rest pain, some individuals can walk no farther after operation than before. To be sure, many have slight increase in walking distance, perhaps from one block to a block and a half or two. Such limited improvement is, however, of little benefit to otherwise active individuals. It may be of real help to those whose demands for walking are limited. A few exceptional patients, in contrast, have received striking improvement. I have treated a small number whose claudication was felt only in the small muscles of the feet. They have been completely relieved of their complaints. It has been reported that some patients with popliteal obstruction and good collateral pathways about the area of the knee have also had complete alleviation. I have had no such experience. Altogether, one would conclude that this operation is safe, often of very real value in relieving or ameliorating ischemic complaints at rest and probably gives the patient some protection against further ischemic disasters, but is not of significant help in certain far-advanced cases and is rarely of real benefit in relieving intermittent claudication. It still has an important place in the management of arteriosclerotic obliterative disease and is the principal surgical measure of value for thromboangiitis obliterans.

Fortunately, the past few years have been demonstrated the feasibility of restoring blood flow through or around obstructed segments of the aorta and the main peripheral arteries. Three methods have been utilized. One is thromboendarterectomy. This is the procedure in which diseased and thickened intima and the obstructing organized thrombus are removed by stripping. The arteriotomies are closed and the patient is left with a thin-walled vessel composed of the medial and adventitial layers. There

can be no doubt that this procedure is often successful. A few surgeons are still employing it extensively, but it has for the most part been abandoned. My experiences were similar to those of others. There was a relatively good percentage of cases in which blood flow was immediately restored. Some of these patients have gone for years and have had no recurrence of the obstruction. Some had immediate failures. Some with initial good results ultimately lost them, as has been true with the grafting procedures as well. The results were in general better in patients who had a relatively short segmental block than in those with extensive occlusion. They also were better when the occlusion was in a large artery, such as the aorta, rather than in a smaller more distal vessel. The second method is the operative resection of the obstructed segment with the end-to-end interpolation of a suitable graft. This procedure, too, was associated with reasonable success but has been abandoned in favor of an end-to-side bypass grafting technic. The excision of the obstructed segment and end-to-end interpolation of a graft has certain disadvantages. For one thing, the area of dissection is rather extensive since one must expose the entire obstructed segment. There is, therefore, greater likelihood that some damage may be inflicted upon good collateral vessels. There is also some evidence to suggest that the continued patency of the artery-graft anastomosis which is naturally limited in size to the circumference of the artery itself is not as high as when an end-to-side bypass grafting procedure is utilized. The latter is the procedure of choice at the present time. It has some real advantages. Relatively small incisions may be utilized since the artery need be exposed and dissected free only at one point proximal to the obstruction and at another distal to it. A graft is passed between the two incisions through a tunnel which is quickly and easily created. The graft is sutured end-to-side to the patent vessel proximal and distal to the obstruction. Since an end-to-side anastomosis is used, the circumference of the anastomosis can be made larger than the circumference of the host artery. Not infrequently one portion of the circumference of the artery is less badly diseased than the rest. It is therefore possible to select the best portion of the artery for the anastomosis. As the necessary dissection is limited there is little likelihood of injuring any collateral artery.

This restorative procedure has a high likelihood of immediate success provided the arterial pathway distal to the obstruction is open and there is a good run-off into which the reopened blood stream can be emptied. For practical purposes the obstructive process must end somewhere proximal to the distal end of the popliteal artery. It has thus far not proved feasible to reopen the arterial pathway when only one or both of the tibial arteries is patent and the entire popliteal obstructed. The question arises whether or not one can tell purely on a basis of history and physical examination if such a procedure is possible. One can more often be right than wrong in such an estimate. For one thing, the presence of adequate collateral circulation at rest is highly indicative of a segmental block with an open distal pathway. A person who complains of intermittent claudication and has a warm well-colored foot with good venous filling is quite likely to have such a condition. Rarely will arteriographic studies and operative exploration reveal the contrary to be the case. This is particularly true if a weak but palpable dorsal pedal or posterior tibial pulse is present in a patient with complete proximal obstruction. In general, the higher the proximal block in the presence of reasonably adequate distal circulation at rest, the more likely is such a situation to prevail. If the abdominal aorta or the common or external iliac is clinically obstructed, the chances are better than if the obstructive process begins in the common or superficial femoral artery and still better than if it involves only the popliteal artery. Such clinical observations are, however, not infallible. Although good circulation in the foot at rest in such cases is likely to denote a favorable situation, the converse is not necessarily true. An ischemic foot, cold, pale and with poor venous filling will far more often than not be found on further study to be the consequence of a completely inadequate distal arterial pathway. Yet exceptions exist and cases are encountered in which restoration of circulation through the main arterial pathways is possible even when gangrene of toes is present. I, and others, have treated such cases in which it has been possible to restore such good blood flow that areas of superficial gangrene have healed or areas of deep gangrene could be treated successfully by amputation of the digit with prompt healing of the stump. Age is of lesser value in predicting the possibility of such a restorative procedure. Restoration of circulation can commonly be achieved when there is some cal-

cification of the affected arteries. Extensive calcification of the arteries of the leg and foot is a bad sign, however, and it is rare under such circumstances to find a situation compatible with successful bypass.

Since the success or failure of these surgical efforts hinges primarily on the patency or obliteration of peripheral vessels distal to the main obstruction, it is important to settle this question before attempting the procedure itself. In some instances it can be solved beyond reasonable doubt by exploration of the artery distal to the known obstruction. If one is dealing with a terminal aortic obstruction, for example, the simple exploration of the femoral arteries prior to laparotomy will provide a reasonably adequate answer. If the femoral arteries are full, apparently relatively free of disease, and well filled by retrograde flow, it is practically certain that the aortic obstruction can be successfully bypassed. If one is dealing with a femoral obliteration, the simple exploration of the popliteal artery and the demonstration that it is in reasonably good condition and well filled with blood gives similar information. These observations are more significant if weak but palpable pulses are felt in the foot. In general, however, it is preferable to obtain more extensive proof of the patency of the distal arterial pathway by arteriography.

Some believe that it is necessary to outline arteriographically the proximal as well as the distal arterial tree. With this I do not agree. It implies in a majority of instances an aortogram since there is no reasonably accurate way of injecting the arterial pathway between the aorta and the common femoral artery. Arteriograms made by femoral injection are surprisingly safe. Aortograms, on the other hand, are unfortunately not free of serious hazards. Deaths have resulted from renal or intestinal ischemia and from other causes. Paraplegia has occurred in a not insignificant number. Altogether, it is my belief that aortography is sufficiently hazardous that its use should be limited to those instances in which it is considered to be of really significant help. It is not difficult clinically to determine the proximal level of the obstructive process. It is my belief, therefore, that the important information to obtain is related to the condition of the distal arterial pathway beyond the obstruction. This can be accomplished with relative ease either by percutaneous puncture of the pulsatile femoral artery or by injection of the femoral artery after its surgical exposure in cases in which there is no pulsation present. The arteriograms should be carried out by the person who is planning to treat the patient. It does not seem to me advisable to have such studies made prior to referral of the patient to the surgeon. All too often the physician does not carry out the study in such a way as to provide the surgeon with the exact information which he wishes. Not infrequently a patient is referred with aortograms which were not necessary and without the essential x-ray visualization of the contrast-filled distal arteries. It is preferable that the arteriograms be performed immediately prior to the contemplated operation. On rare occasions a thrombus may develop at the site of the arterial puncture. The complication can be obviated if the operation is carried out immediately thereafter. Furthermore, the obliterative process may change in certain individuals with remarkable rapidity and the situation today may not be precisely the same as it was two, three or six weeks beforehand. The performance of arteriography without anesthesia is often attended by considerable pain. If the pain is of sufficient degree the patient moves his limb and the arteriogram is unsatisfactory. Perhaps the vasodilatation which occurs with anesthesia may also be of some benefit in the avoidance of ischemic complications. It is my policy to admit the patient to the hospital and after suitable study to schedule him for arteriography and possible grafting procedure. The patient understands that if the arteriogram reveals a situation indicative of a reasonable chance for success he will be immediately subjected to a bypass grafting procedure. If, on the contrary, the arteriogram reveals a completely inadequate run-off it is understood that no operation will be carried out, or a sympathectomy will be performed if the latter procedure seems indicated. Usually the arteriogram is performed under spinal anesthesia and the patient can be informed of the results and of the operative possibilities as soon as the study is completed. The x-ray exposure is properly calculated to permit an exposure time of five seconds and the entire extremity is x-rayed. With the long exposure time one is able to deliniate not only the proximal but the distal portions of the arterial tree. The arteriograms are reasonably accurate in denoting the actual situation existing. In general, however, the arteriograms look somewhat better than the vessels themselves do at the

time of exploration. Occasionally one meets with a situation in which there is a fairly good arteriogram but in which the lumen of the artery is only a thin ribbon-like opening and the artery is for all practical purposes almost obliterated.

At operation one first exposes the distal artery. If it is in reasonably good condition one can be almost certain of an immediate success. However, if the segment is badly diseased and the lumen small, one can proceed with the operation knowing that the chances of an initial good result are somewhat reduced but are still surprisingly good. The other end of the graft is then implanted in the artery proximal to the obstruction at some level where the pulse is good and the artery is in relatively good condition. It is better to pick a site somewhat proximal to the obstruction rather than to implant the graft into a badly diseased segment immediately adjacent to the obstruction. Sometimes it is necessary to do a thromboendarterectomy at the site of the proximal anastomosis because of the presence of extreme calcification and intimal disease. This is particularly true in instances in which the graft is inserted into the aorta itself. It is desirable, however, to suture the graft to a segment which is sufficiently free of disease so that a local thromboendarterectomy is not necessary.

It is not possible at the present time to state with finality what type of graft is best to employ. There can be no doubt that fresh autogenous vein grafts can be used successfully. Unfortunately, however, it is frequently impossible to obtain such a graft of adequate length and size. For this reason, such grafts are not commonly utilized. Preserved arterial homografts have been used with general satisfaction. They are usually preserved by freeze-drying after sterilization with ethylene oxide or beta propiolactone. They are somewhat difficult to obtain in adequate numbers. This is particularly true of peripheral arterial segments since most pathologists are more unwilling to secure long segments of peripheral arteries than segments of the aorta which is always exposed in the routine thoracoabdominal postmortem exploration. They are pliable, of proper size, and are easily sutured to the host vessel. They are, however, not viable structures and serve principally as a scaffold or tube about which the host lays down a new fibrous blood vessel with an intimal-like lining. Experimentally they present a good gross appearance during relatively short periods of observation. As time passes on they demonstrate gross and microscopic evidence of arteriosclerotic-like changes with deposition of calcium and lipids. As the time interval lengthens, they also tend to show fragmentation of the elastic layer which is the only layer of the original graft which persists for a long time. In experimental hypercholesterolemia they have been demonstrated to have a particular predisposition towards lipid deposition. Tubes constructed of inert plastic materials have been shown experimentally to serve quite well. Although they are not quite as easy to suture to the host vessel as is a homograft, this presents no real difficulty. They rapidly become incorporated in a new fibrous vessel with a smooth intimalike lining membrane. During long periods of observation they remain remarkably free of the degenerative changes which are so commonly seen in homografts. A variety of plastic materials have been used with eminent success as substitutes for the thoracic or abdominal aorta. In such situations one is not concerned with possible kinking or wrinkling of the graft since the vessel is straight and bending is not necessary. In the extremity, however, one must have an arterial substitute which does not give trouble because of bending or wrinkling with movement of the extremity itself. This problem has been obviated in the Edwards-Tapp graft which is a woven nylon tubular structure prepared in such a way that it is crimped in an accordion-like fashion. These grafts do not wrinkle or become obstructed with bending. Most of our experiences with peripheral arterial substitution have been with this type of graft. It has proved altogether satisfactory. Szilagyi has recently developed a new plastic tube prepared of fibers treated so that they are wave-like rather than straight, rather like the fibers used in the manufacture of stretch hose. Tubes so constructed can be bent without wrinkling and I am told by the few who have used them fairly extensively that they are eminently satisfactory. Perhaps they will prove to be the best type of graft available at the present time. There is every reason to believe that plastic prostheses better than those currently available will be developed in the future. Those now at hand, nevertheless, seem quite satisfactory. A number of surgeons with large experiences prefer plastic prostheses, as I do. Still others who do a great deal of such work are utilizing plastic grafts more and more and homografts less and less. Undoubtedly a long period of time will be required before one can ultimately answer

objectively the question whether plastic arterial substitutes or preserved homografts are better. Taking everything into consideration, it is my belief at the moment that the plastic substitutes are preferable.

Assessment of the final results of bypass grafting procedures for arteriosclerotic obliterative disease is difficult for a number of reasons. Although considerable experience has been obtained, most observations extend over a relatively brief period of time. There is considerable variability in the clinical material, not only from the standpoint of age and arteriosclerotic process of the patients treated, but also from the standpoint of the local situation. It includes bypassing of different portions of the arterial tree from the aorta to the popliteal arteries. The length of the graft used has varied tremendously. The status of the distal arterial tree has differed widely. Furthermore, there has been wide variation with regard to the state of the artery at the site of the anastomosis, particularly at the site of the distal anastomosis. Some grafts have been attached to relatively normal arterial segments, others to badly diseased ones. Perhaps the chief limiting factor in permitting a clear evaluation at this time is the variability of the arteriosclerotic process in the patient himself. In some patients limited segmental obstruction apparently develops and over a period of many years they exhibit no demonstrable spread of the arteriosclerotic obliterative process. In others, the disease is more diffuse and progression much more rapid. Because of these circumstances, it is unlikely that a final answer to the question of the ultimate results can be obtained for some time.

Certain impressions, however, seem valid at the moment. Regardless of the length of the graft necessary to bypass the obstruction, there is an almost certain likelihood of immediate restoration of peripheral pulses and relief of symptoms provided one is dealing with a segmental obstruction, a good distal pathway and relatively normal arterial segments into which the graft can be implanted. Immediate failure under such circumstances must be regarded as a technical error. Surprisingly enough, the percentage of cases in which an immediate restoration of blood flow is established is extremely high even when the distal pathway is somewhat compromised and the anastomosis must be made to an obviously badly diseased artery. Immediate success is obtained in almost all instances even if only one tibial vessel is demonstrated to be patent and even if the distal anastomosis must be made to a narrowed, thickened, badly diseased segment of artery. It is my experience that one commonly accomplishes such an anastomosis with the feeling that there is practically no likelihood that it will succeed, only to find that blood flow about the obstructed segment is immediately restored. The principal quandry concerns the long term results. There is no doubt in my mind that the longer patients who have had an initially successful bypass procedure are observed, the greater will be the percentage in whom the good result will ultimately be lost. Thus far, however, the late failures, although constituting a real problem, have not occurred so often as to discourage one from continuing efforts to bypass areas of segmental obstruction.

Two types of late failures have been observed. One is extremely rare. After leaving the hospital with good peripheral pulses and complete relief of symptoms, two patients have returned some months later with a false aneurysm at the site of either the distal or the proximal anastomosis. In both cases I believed that an adequate explanation for this complication was available. In one patient the plastic graft had been torn during the suture anastomosis. Instead of amputating the graft back beyond the area of injury and re-implanting it, completion of the anastomosis was accomplished in such a way as to prevent leakage through the area of injury. In the other patient, who had a graft interpolated between the common femoral artery and the popliteal artery, the pulsating hematoma developed after the patient tried to break in a new horse by riding it bareback. It seemed that the pressure on the inner aspect of his thigh had partially sheared the graft away from the host artery. In both instances, a graft was successfully re-implanted. In both, however, a second pulsating hematoma developed sometime later on. In the first patient, the second pulsating hematoma again occurred at the proximal anastomosis. In the other, whose original difficulty was at the distal anastomosis, the second pulsating hematoma developed at the proximal anastomosis. The fact that in these two exceptional cases both patients had not only one but two pulsating hematomas would make one wonder whether or not there was some peculiar intrinsic difficulty with healing. Tempting as this explanation might be, it seems hardly tenable in view of the fact that the vast majority of patients have good healing between the vessel

and the graft regardless of the extensiveness of the disease process in the host artery at the site of implantation. This late complication is an extremely rare one and perhaps it can be eliminated completely.

The second late complication, which is more commonly encountered, is a loss of peripheral pulses. I have had a number of patients who after periods of from six months to a year or more have lost the good result they had and in whom previously present peripheral pulsations have disappeared. In a few such cases no further study has been possible and the mechanism of the failure is obscure. In most of them, however, information is available to suggest that it results not from a primary graft failure but from extension of the obliterative disease itself. Several examples may be cited. One patient left the hospital with excellent popliteal, dorsal pedal, and posterior tibial pulses after a bilateral common iliac-superficial femoral bypass procedure. Approximately six weeks later symptoms returned in one extremity. On re-exploration it was found that the common iliac artery on that side was completely occluded from its origin down past the site of the proximal graft anastomosis to the level of the original obliterative process. In this case it had been necessary to perform a local thromboendarterectomy before performing the anastomosis. In retrospect this obviously represented an error in judgment. The original graft should, instead, have been affixed to the aorta itself. At the second operation a graft was implanted proximally into the aorta and distally into the superficial femoral artery and the patient has now had for approximately fifteen months relief of symptoms and good pulses in both lower extremities. More commonly there is evidence of extension of the obliterative process distally. One patient who had an excellent result after resection of the occluded terminal aorta and interpolation of an aortic-bilateral common iliac graft had a return of symptoms seven months later. On re-exploration the graft was found in excellent condition as were the common iliac arteries for a distance of approximately 1½ or 2 cm. distally. Both, however, had undergone complete occlusion in their distal segments. Another patient had been treated by interpolation of a long bypass graft between the external iliac and the terminal portion of the popliteal artery. The external iliac artery was normal in appearance. The popliteal artery was completely obliterated down to its distal segment underneath the head of the gastrocnemius muscle. In this area it was patent but obviously diseased. The patient was relieved of his symptoms and had a good posterior tibial pulse. Five months later he experienced the return of intermittent claudication and the posterior tibial pulse was no longer palpable, although the graft pulsated well. Two weeks afterwards marked ischemia of the foot suddenly developed, and the foot became cold, numb and pale. The graft was still pulsating well when he arrived in the hospital. At operation a fresh thrombus was found in the very distal portion of the graft, while the remainder was patent. The bifurcation of the popliteal artery just beyond the anastomosis was completely occluded. Such a train of events, it seems to me, can be interpreted only on the assumption that the artery distal to the anastomosis became occluded two weeks prior to the time of admission and that the occlusive process extended proximally so as to include the area of outflow from the graft itself on the day of admission. Still another patient was admitted to the hospital with a great deal of rest pain, with superficial gangrene of the end of the second toe, and with deep gangrene involving the distal phalanx of the third toe. He had a large varicose saphenous vein on that side. The saphenous vein was used as an autograft and was sutured end-to-side to the patent popliteal artery below and to the common femoral artery above the obstructed segment. An excellent dorsal pedal pulse developed, he lost his rest pain, and there was good circulation in the foot. The area of superficial gangrene healed. The third toe was amputated and the stump healed promptly. He was relieved of all his complaints for a period of six months when he had a return of intermittent claudication and rest pain. Examination at that time revealed no pulse in the dorsal pedal artery, the popliteal artery or in the graft itself. At the time of his original treatment there had been a bounding popliteal pulse in the opposite extremity and an excellent dorsal pedal pulse. Now the dorsal pedal pulse in that limb was gone and the popliteal pulse could be felt to pulsate only extremely weakly. It was obvious that during this six months' interval he had undergone rapid progression of his arteriosclerotic process in his better extremity and it seemed a reasonable assumption that the same had taken place on the treated side and accounted for the late failure. In all instances in which an early good result has been lost after a period of time and in

which sufficient data are available, there seems to be positive or presumptive evidence that the late failure occurred primarily because of extension of the arteriosclerotic process rather than because of thrombosis of the graft itself.

It seems to me that this progression of the disease constitutes the principal limiting factor with regard to long term success in those patients who initially have restoration of good flow from a bypass grafting procedure. Late failures are noted less frequently in cases in which the distal arterial tree is relatively free of disease and the anastomoses are performed in segments which are widely patent and little involved in the arteriosclerotic process. They occur more frequently when the distal vessels are partially obliterated or narrowed and the anastomoses must be made at levels where the lumen is small and the arterial wall thickened and irregular. They also seem more prone to develop the more distally the bypass must be made. Some of these patients have an elevated serum cholesterol, some have normal or low normal serum cholesterol values. For what it may be worth, it has lately been recommended that an effort be made to combat the problem of abnormal blood lipids by diet and medication in all instances in which the serum cholesterol has been found to be abnormally high or in a relatively high normal range. If we learn to prevent the progress of the intrinsic arteriosclerotic disease we shall almost certainly increase the percentage of patients who have a good long term result following an initially successful bypassing procedure. Not only should efforts in this direction be continued, but it is also very important that surgically treated patients be followed up for long periods of time and long term results be recorded in the literature.

CONCLUSIONS

An effort has been made to summarize the present status of surgical efforts to treat the ischemic peripheral disorders. Sympathectomy has proved to be a safe and valuable procedure. It has certain limitations, particularly in far advanced obliterative disease and in its general lack of significant benefit with regard to intermittent claudication. Of the procedures available for restoration of blood flow through or about obstructed arterial segments, end-to-side bypassing grafting procedures appear to be the best. Such efforts result in a high percentage of initial success provided there is a reasonably satisfactory distal run-off. Long term results are not as good as the immediate results apparently principally because of extension of the arteriosclerotic occlusive process.

End of Symposium on Peripheral Vascular Diseases

Clinical Studies

Thrombotic Thrombocytopenic Purpura*

A Report of Three Cases

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The purpose of this report is to add three additional instances of thrombotic thrombocytopenic purpura to those previously reported, and to suggest a pathologic concept based on newer observations made in this material. The third case observed also afforded the opportunity to confirm the suggestion of Morey, White and Daily [5] that biopsy of a lymph node selected at random may afford a ready means of diagnosis.

Since 1925, when Moschcowitz [1] first reported this disorder, sixty-nine additional acceptable cases have been recorded in the literature, chiefly the American literature. In almost all instances the patients reported have had the typical clinical course with thrombopenia, purpura, anemia, high fever, cerebral manifestations and an almost always rapidly fatal course. In only a few instances has the diagnosis been made antemortem. No clear-cut generally acceptable etiologic factors have emerged, nor is any offered here. In twenty instances, including the three presented herein, a "leukemoid" reaction has been noted in the peripheral blood. Another observation, noted in twenty-two instances including the three presented in this paper has received little comment in the literature. It is the finding of what appears to be megakaryocytes, in large number in some instances, in the smaller pulmonary blood vessels. Also observed in all three instances reported herein is the occurrence of megakaryocytes in organs other than the lungs. Only three other reports mention this observation and these were observed in the spleen by Cooper et al. [3] and Trobaugh et al. [4], and in the kidney by Wyatt and Lee [26]. In the cases herein reported megakaryocytes were observed in several organs, including the kidneys, pancreas, lymph nodes and heart. Not only were the megakaryocytes observed in arterioles, as in the renal glomerular loops, but also as whole or fragmented megakaryocytes in the thrombotic lesions. The latter occurrence was most strikingly seen in the third instance reported.

CASE REPORTS

Case 1. The patient, a thirty-seven year old Negro housewife was admitted to the hospital on June 24, 1952, in a confused semiconscious state. The history, obtained from the husband, revealed that the patient had been well until ten days before admission, when he noted his wife to be pale and mentally sluggish. Three days later the patient fainted while sunbathing at a local beach. There was a history of antisyphilitic therapy a few years earlier. On admission, the patient appeared well nourished, pale, toxic, confused and restless. The temperature was 102°F.; pulse, 110 per minute; and the blood pressure 150/70 mm. Hg. Except for sluggishly reacting pupils, hypoactive deep reflexes and profuse vaginal bleeding, physical examination revealed no abnormalities. Laboratory data revealed a marked anemia of 1.5 million red blood cells and 11,800 white blood cells per cu. mm. Five per cent normoblasts and a marked decrease in platelets were noted in the differential smear. The platelet count reported on two occasions was 11,000 and 14,000 per cu. mm., respectively. Urinalysis revealed albuminuria, many red blood cells and granular casts. Slight jaundice was noted; the icteric index was recorded as 15. Blood studies, including bleeding and coagulation times, test for sickling, fragility test, Coombs' test, serum calcium, phosphorus and alkaline phosphatase showed no abnormalities. The prothrombin time was sixteen seconds. Reticulocyte counts of 3.3 and 4.9 per cent were obtained. An erythrocyte sedimentation rate (Westergren) of 108 mm. in one hour was recorded. A spinal tap yielded clear fluid containing thirty-two white blood cells per cu. mm. A colloidal gold test was strongly positive. A sternal marrow aspiration was negative

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except for a low total nucleated cell count and a moderate increase in the nucleated red blood cells. Vaginal bleeding ceased and then marked frank hematuria was noted. Many petechiae appeared in the skin of the arms and the visible mucous membranes. The patient died fifteen days after admission.

At autopsy, gross findings revealed the presence of small petechial hemorrhages in the breast, liver, peritoneum, fascia, muscle and skin. A right subdural hemorrhage was noted, with yellowish discoloration of the dura and meninges. A small cerebral hemorrhage in the region of the right basal ganglia was also found. Histologically, typical platelet thrombi were noted in the heart (Fig. 1), liver, adrenals (Fig. 2), pancreas, kidneys, brain and bone marrow. Megakaryocytes were clearly demonstrated in the lumens of venule size in the pulmonary alveolar walls. (Figs. 3, and 4.) What appeared to be another megakaryocyte was noted in a glomerular capillary of one kidney. (Fig. 5.)

Case II. This forty year old white housewife was admitted to the hospital in a comatose state on June 2, 1956, with a five-day history of anorexia, malaise, nausea and progressive weakness. A brownish discoloration of the urine had been noted for about one week. On physical examination on the night before admission the skin was noted to be slightly icteric. On admission the gums bled slightly. Several small ecchymoses were noted over the upper and lower extremities and the trunk. The liver and spleen were not palpable. The temperature was 100°F.; pulse, 100 per minute; and respiration, 22 per minute. The blood pressure was 124/74 mm. Hg. A blood count revealed 5.4 gm. per cent of hemoglobin, 1.8 million red blood cells and 7,400 white blood cells per cu. mm. Numerous normoblasts, few myelocytes and promyelocytes were noted in the smear. Platelets were found to be markedly decreased. Examination of the urine revealed a 4-plus albumin, a trace of glucose and 3 to 5 red blood cells and 3 to 5 white blood cells per high power field. A serum non-protein nitrogen was recorded as 37 mg. per cent, and CO_2 combining power was 18 mEq./L. The patient was given a blood transfusion, ACTH and cortisone therapy which were of no avail. She died the following day.

The gross findings at autopsy revealed many petechiae, especially in the lungs, kidneys and myocardium. In the latter small areas of yellowish discoloration as necroses were also noted, as in Case I. The microscopic examination again revealed typical thrombotic lesions in the heart, liver, pancreas, bone marrow, adrenals (Fig. 6) and kidney. (Fig. 7.) Few megakaryocytes were noted in the venules of the pulmonary alveolar walls. (Fig. 8.) No thrombotic lesion was noted in the sections of the lung.

Case III. A twenty-three year old Negro female houseworker was admitted to the Mount Vernon Hospital on December 8, 1956, following a visit to her dentist who had observed petechial hemorrhages in the mucous membranes of her mouth and referred the patient to her physician who in turn suggested hospitalization. In May 1956, the patient had been hospitalized elsewhere for menorrhagia and had undergone a uterine curettage. At this time a blood count was recorded as 8.4 gm. per cent hemoglobin, 2.9 million red blood cells and 4,500 white blood cells per cu. mm. The differential count showed 54 per cent polymorphonuclears and 46 per cent lymphocytes. For some time prior to the patient's last hospital admission she had had severe headaches for which she had taken bufferin® with occasional relief. She had also used an unnamed hair dye. The past history was non-contributory. At the age of nineteen the patient had had a normal pregnancy and an uneventful delivery.

Physical examination on admission revealed an apprehensive, slender, moderately well nourished Negro woman. Small petechiae were noted in the mucous membranes of the mouth and on the skin of the arms, abdomen, thighs and legs. On admission the blood pressure was 110/80 mm. Hg. The temperature was 100°F.; pulse 80 per minute; and respirations 20 per minute. The heart and lungs were normal to percussion and auscultation. The liver and spleen were not palpable and no masses were felt in the abdomen. The reflexes were normal. A blood count revealed 8.0 gm. per cent; hemoglobin, 3.1 million red blood cells and 4,700 white blood cells per cu. mm. with 1 per cent staff cells; 47 per cent polymorphonuclear neutrophils; 1 per cent basophils; 42 per cent lymphocytes; and one further unidentified blast cell. The platelets were recorded as 12,600 per cu. mm. The bleeding time was seven minutes and five seconds. The coagulation time was four minutes and thirty seconds. Clot retraction was incomplete in twenty-four hours. A Coombs' test, L.E. test, sickle cell preparation and fragility test were all negative. A reticulocyte count was recorded as 11.9 per cent. A urinalysis revealed a specific gravity of 1.020, 4-plus albumin, with glucose, and acetone negative. The urine sediment was negative. A sternal marrow aspiration on two occasions was essentially negative. Beginning on December 18 the blood counts revealed further developing anemia, with few metamyelocytes and normoblasts observed on smear. The following day the patient had an episode of severe apprehension and restlessness followed by confusion, disorientation and screaming. The temperature at this time was 103.8°F. The patient was believed to have thrombotic thrombocytopenic purpura and a left cervical lymph node was excised for diagnosis. The typical thrombotic lesion was noted in the node (Fig. 9) and the diagnosis thus confirmed. The patient, who had been receiving cortisone-meticortin therapy, was then given increased doses without improvement. The vaginal bleeding and further development of petechial hemorrhage did not

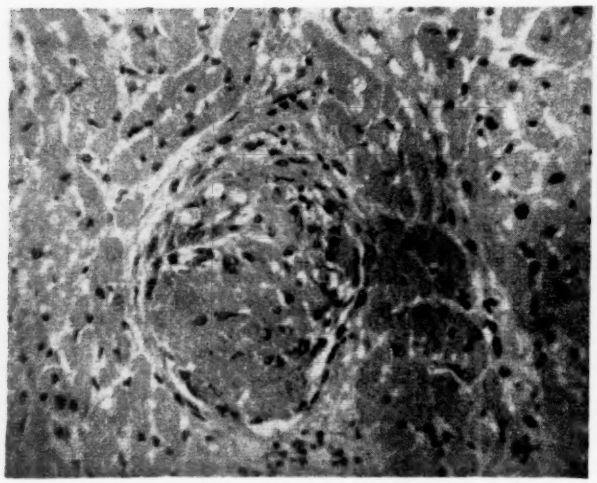


FIG. 1. Case 1. Typical thrombotic lesion in the myocardium.

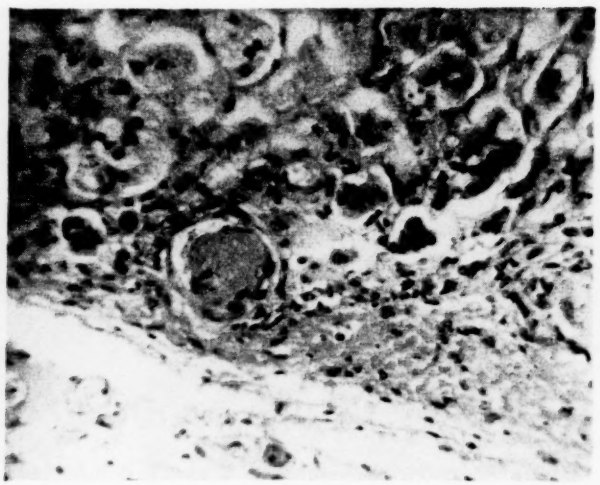


FIG. 2. Case 1. Thrombotic lesion in arteriolar-capillary junction of the adrenal cortex.

abate. The patient's condition became worse and she died on January 18, 1957.

At autopsy, performed on the day of the patient's death, the most striking gross findings were the petechial hemorrhages in the skin and mucous membranes, and especially the many petechiae in the epicardium and endocardium. Few petechiae were seen in the pons such as those noted in the region of the basal ganglia of the patient in Case 1. In addition, small, yellowish, necrotic myocardial alterations were observed, as noted in both previous instances. Clotted blood was noted in the uterine cavity. The lungs were edematous, with bronchopneumonia of the bilateral lower lobe confirmed microscopically. The lymph nodes of the right supraclavicular fossa, both axillas and both inguinal areas, and the mesenteric and mediastinal lymph nodes were not enlarged. A sampling of all lymph nodes of these areas, fifteen nodes in all, was taken for histologic study.

The histologic study proved to be most rewarding. All lymph nodes revealed the typical thrombotic lesions which were most numerous however in the larger nodes. All tissue studied, with the exception of the uterus, ovaries, urinary bladder and gastrointestinal tract revealed the thrombotic lesions. These included (in addition to the lymph nodes) the lungs, brain, pituitary, liver, spleen, kidneys, pancreas, thyroid, parathyroid, striated muscle, adrenal gland (Fig. 10), and especially the myocardium which contained the most numerous lesions. The lungs in this instance contained a large number of megakaryocytes, which could be found without difficulty. (Fig. 11.) An occasional megakaryocyte could also be seen in the vessels of the heart, pancreas and in one lymph node. In two instances the megakaryocytes could readily be identified in fresh thrombotic vascular lesions in the myocardial vessels. (Figs. 12 and 13.)

Possibly because this patient lived the longest, the

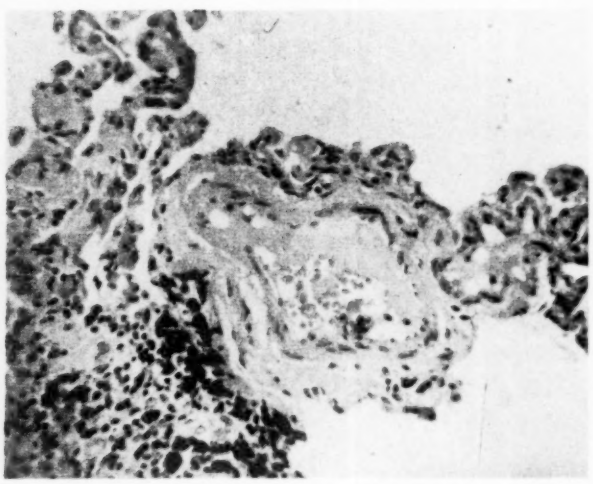


FIG. 3. Case 1. Megakaryocyte in pulmonary vessel.

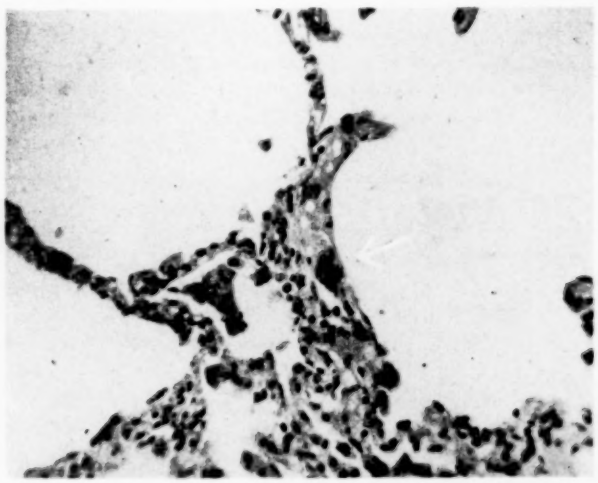


FIG. 4. Case 1. Megakaryocytes in pulmonary vessel.

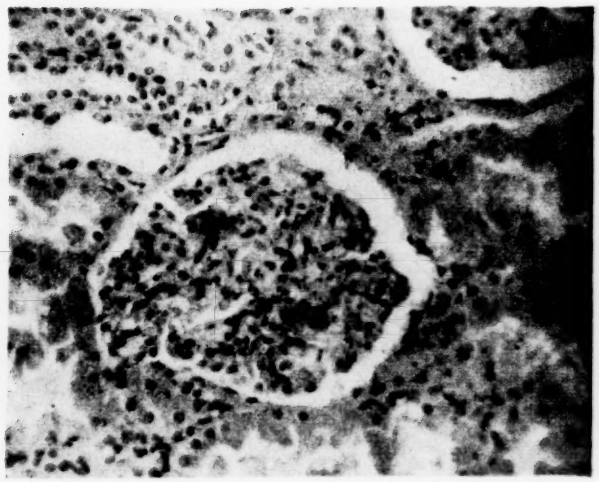


FIG. 5. Case I. Megakaryocytes in glomerular capillaries.

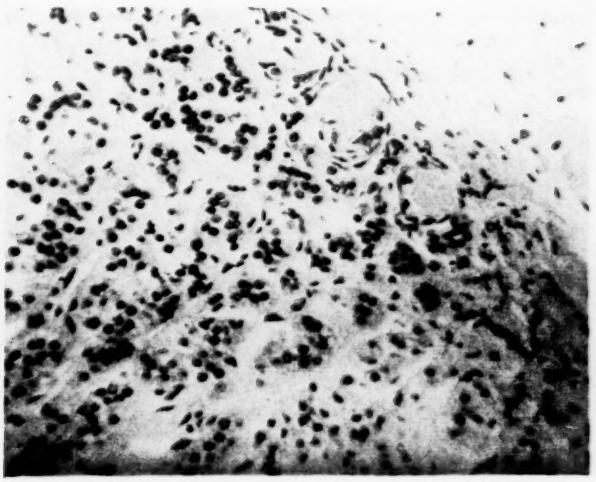


FIG. 6. Case II. Thrombotic lesion in arteriolar-capillary junction of the adrenal cortex.

vascular lesions were more varied in appearance. The more recent lesions were granular fibrin thrombi containing nuclear fragments, sometimes with the appearance of platelets or containing recognizable megakaryocytes, as already described. The older lesions consisted of a more uniform mass presenting a more hyaline appearance. Finally, recanalization was observed in three thrombotic lesions. (Fig. 14.)

COMMENTS

The material presented substantiates the suggestion of Morey, White and Daily [*5*] that random biopsy of the lymph nodes may give ready confirmation of the diagnosis.

The findings appear to indicate that the megakaryocytes noted in the pulmonary vessels were released from the bone marrow under some unknown stimulus. In the lungs they may disintegrate wholly or in part, or they may pass intact through the pulmonary capillary bed and enter the peripheral circulation. Then, either as platelet masses, large fragments of megakaryocytes or intact megakaryocytes the typical thrombotic lesions are formed at the arteriolar-capillary junctions. This view is opposed to the original suggestion of Moschcowitz [*1*] that the thrombi are composed of erythrocytes, but supports the concept of Baehr, Klemperer and Schifrin [*2*] that platelets are incorporated in the thrombi, although the assumption of these authors that the process is of an intrinsic vascular nature, possibly of the "collagen" disease type, is not confirmed. Based on the material herein presented I am of the opinion, also held by others (Trobaugh et al. [*4*], Muirhead et al. [*6*], Fitzgerald et al. [*7*] and Singer et al. [*8,9*]) that the

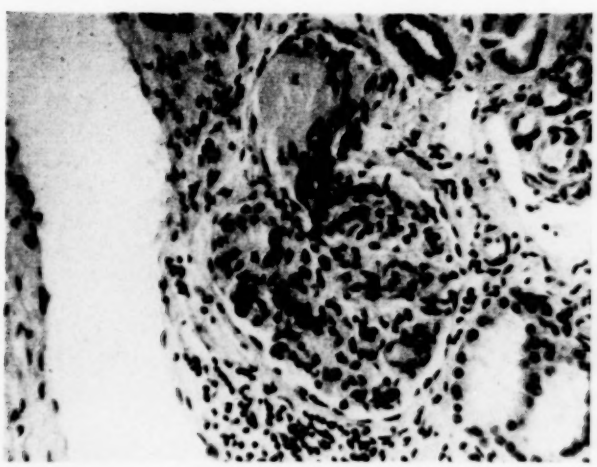


FIG. 7. Case II. Thrombotic lesion in afferent arteriole of a glomerulus.

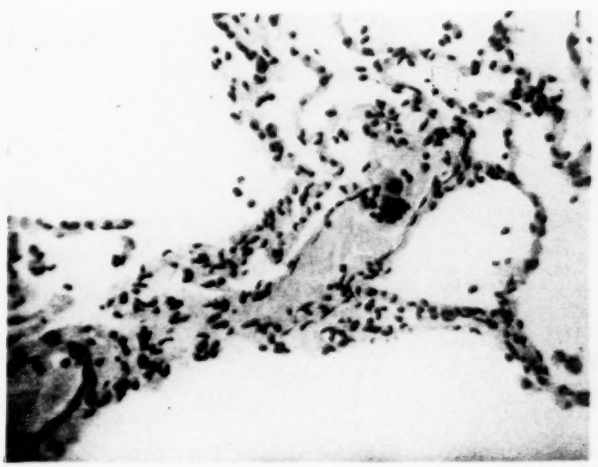


FIG. 8. Case II. Megakaryocyte in pulmonary vessel.

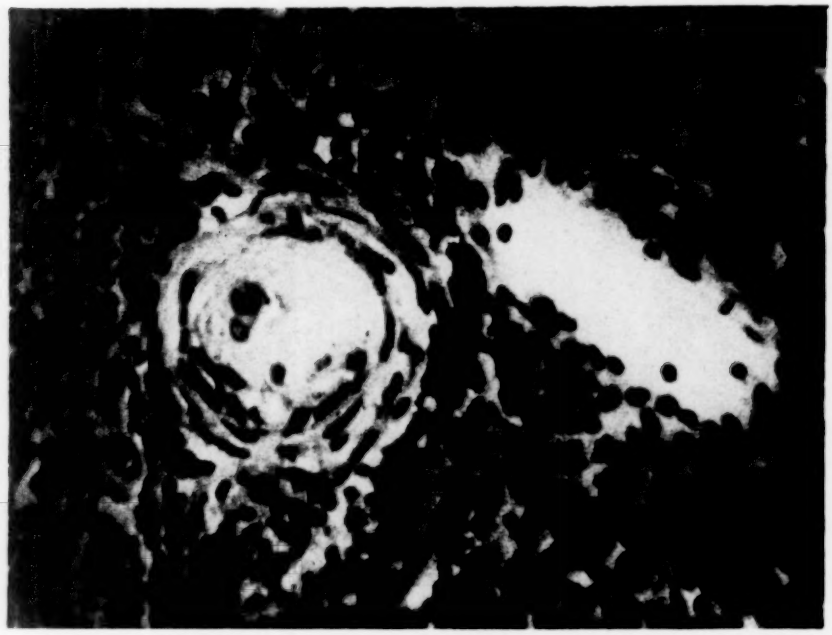


FIG. 9. Case III. Thrombotic lesion in biopsied left cervical lymph node. Note fragmented nuclear masses in this thrombus.

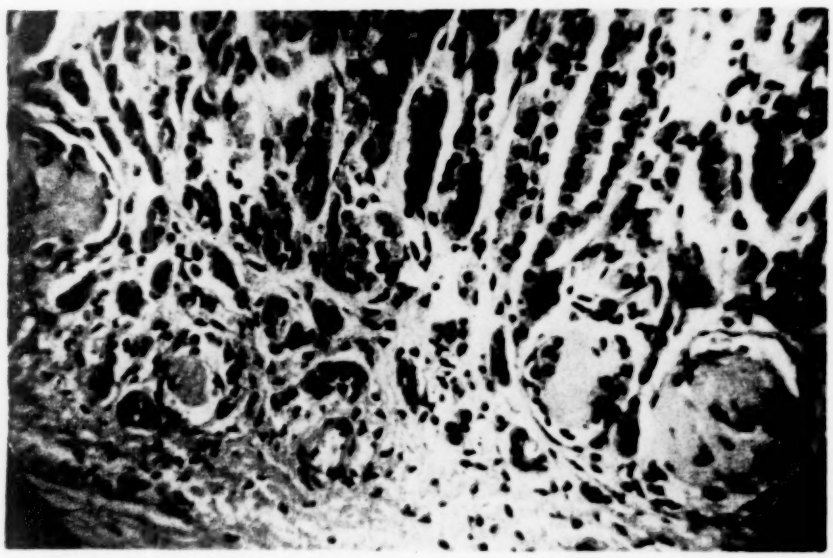


FIG. 10. Case III. Thrombotic lesion in arteriolar-capillary junction of the adrenal cortex.

vascular changes are secondary to the thrombotic phenomena. This is based chiefly on the observation that all other vessels examined were normal and only the thrombotic vessels were altered. The finding of megakaryocytes in the vessels of the pulmonary alveolar walls is not common and has been reported in the past with little comment. It was first reported in 1893 by Aschoff [*10*] who believed them to be embolic. Trobaugh et al. [*4*] first noted them in thrombotic thrombocytopenic purpura. Brill and Halpern [*11*] apparently observed this phenomenon with some frequency in acute leukemias, purpuras, sepsis and tuberculosis, to mention a few instances. Seebach and Kernohan [*12*] also report this finding in all instances of bacterial endocarditis studied. No thrombotic lesions were described by these observers but recently Husebye, Stickney and Bennett [*13*] reported the occurrence of platelet thrombi in three instances

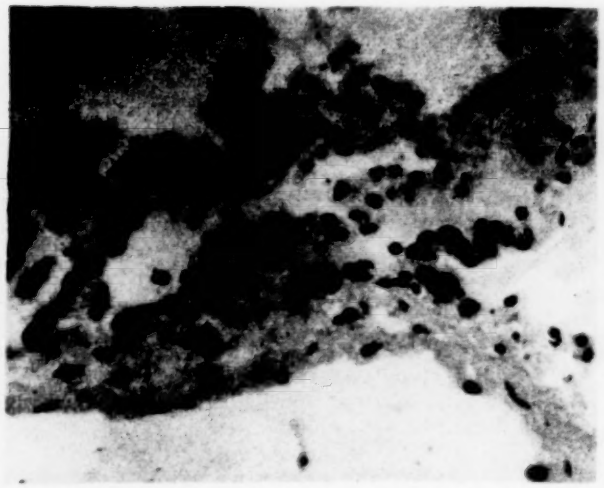


FIG. 11. Case III. Many megakaryocytes in alveolar wall vessel.

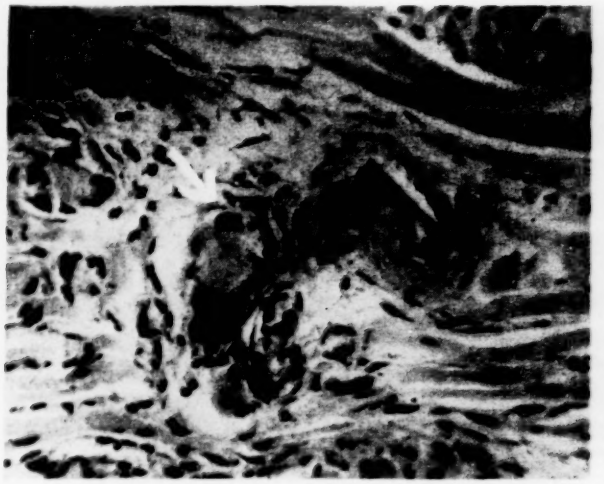


FIG. 12. Case III. Granular thrombotic lesion with megakaryocyte in myocardium. Note hyaline character of adjacent thrombotic lesion.

of leukemia, two of acute leukemia and one of chronic myelogenous leukemia; no mention was made of pulmonary megakaryocytes. Pagel [*14*] has also reported similar thrombotic lesions in three instances of subacute bacterial endocarditis and one of tuberculosis septicemia. Also, Symmers and Gillett [*15*] have reported finding the typical thrombotic lesions in a patient with malignant hypertension, polyarteritis nodosa, silicotuberculosis and sarcoidosis; again no reference was made to megakaryocytes in the lungs. Although the evidence is still inconclusive, the reports cited would suggest a possible multiple etiology of these lesions.

One additional clinical laboratory finding which occurs with significant frequency, and has been commented upon before, lends some support to the concept expressed here. It has been observed in twenty of all reported cases that a leukemoid reaction was present in the peripheral blood. In most instances this consisted chiefly of the finding of nucleated erythrocytes, with occasional myelocytes, promyelocytes and metamyelocytes. This seems to suggest bone marrow stimulation in these cases, which may also well account for the release of megakaryocytes from the marrow. I made an unsuccessful search for megakaryocytes in the peripheral blood of two patients with proved cases of thrombotic thrombocytopenic purpura.

The vascular changes observed in Case III indicate that the presumed stimulation of the

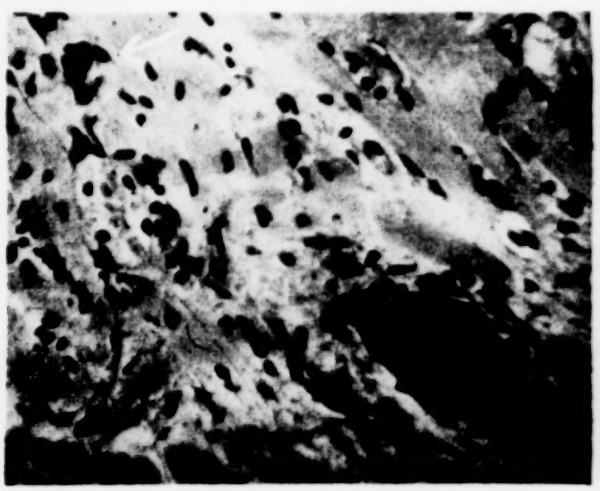


FIG. 13. Case III. Thrombotic lesion with megakaryocyte in myocardium. Note hyaline character of second thrombotic lesion.

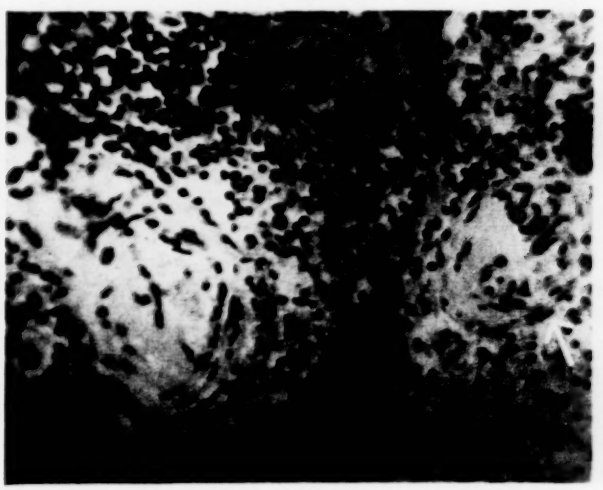


FIG. 14. Case III. Recanalization of thrombotic lesion in a lymph node.

bone marrow may be intermittent to explain the finding of fibrin, hyaline and recanalized thrombi.

SUMMARY

1. Three additional cases of thrombotic thrombocytopenic purpura are reported.

2. The possibility of diagnosis of this disorder by biopsy of a lymph node selected at random is confirmed.

3. Evidence is presented that platelets and megakaryocytes which have passed through the pulmonary circulation are incorporated in the thrombotic lesions.

4. A "leukemoid" reaction is observed with great frequency in thrombotic thrombocytopenic purpura, suggesting the possibility of a bone marrow stimulation as the basic etiologic factor.

5. The process may well be a symptom rather than a disease entity, since pulmonary megakaryocytosis occurs in leukemias (in which thrombotic lesions also have been observed), bacterial endocarditis, sepsis and tuberculosis.

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The Appearance of New Cardiac Murmurs in Patients Having Rheumatic Heart Disease with No Concomitant Evidence of Rheumatic Activity*

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Clearly defined episodes of acute rheumatic carditis may be followed by a number of different clinical courses. In rare instances of fulminating activity the episode may terminate in death from cardiac failure within a few days or weeks. In other instances, also relatively rare, the rheumatic fever may continue from the acute stage into a state of chronic activity lasting for months or years, with ultimate inactivity of the rheumatic process or death of the patient. Finally, in the majority of cases the rheumatic fever may subside, with clinical and laboratory evidence of complete quiescence of the inflammatory process, leaving the patient with what is considered to be inactive rheumatic heart disease or with no heart disease. Of this last-named group a certain number of patients undergo subsequent well-defined episodes of rheumatic fever, often with an increase in the extent of cardiac damage. This fraction has been substantially reduced by the prophylactic use of sulfonamides or antibiotics.

In all these major groups of patients with rheumatic fever the involvement of cardiac tissue is associated with recognized episodes of rheumatic fever. Other cases have been indicated, however, in which progressive cardiac damage could not always be associated with known episodes of this disease. Thus Bland and Jones found that of patients recovering from acute episodes of rheumatic fever without detectable heart disease, evidence of cardiac damage was present in 27 per cent after ten years [*1*] and in 44 per cent after twenty years [*2*]. In one third of these patients there was no known episode of rheumatic fever in the intervening decades. Similarly, in a group of patients whose initial episodes of rheumatic fever or chorea had left no signs of cardiac damage Ash [*3*] found evidence of heart disease after ten years in 23 per cent, and of these patients one-sixth had had no known rheumatic recrudescence. In these studies not all the patients could be observed continually by the investigators during the periods referred to.

In the course of our long-term studies of rheumatic heart disease four children were observed in whom evidence of extension of heart disease was found not in association with an episode of rheumatic fever. In these children a new cardiac murmur appeared while they were being observed at regular intervals during presumed quiescence of the rheumatic disease. This paper will present clinical data, the measurements of three acute phase reactants, and the results of two streptococcal serologic tests in these patients, together with comparative observations made in groups of patients with other variants in the clinical course of rheumatic fever.

METHODS AND MATERIALS

Clinical Material. The patients included in this study were observed as in-patients on the pediatric wards of The Children's Hospital of Philadelphia and The Philadelphia General Hospital. They were also

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followed up as out-patients in the respective Rheumatic Fever Clinics of these two hospitals, and during periods of convalescence at The Children's Seashore House for Invalid Children. They were selected from a group of several hundred rheumatic subjects studied systematically in the course of investigations carried out by the Rheumatic Fever Research Laboratory of The Children's Hospital of Philadelphia from 1942 to the present.

Patients in four clinical categories were selected for study: I. *Subclinical rheumatic activity:* This group consists of four patients with rheumatic heart disease in whom the disease was considered on clinical grounds to be in a quiescent state but in whom the finding of a new cardiac murmur gave evidence of recent activity of the disease. II. *Doubtful rheumatic activity:* This group consists of two children in whom the activity of rheumatic fever was in doubt until roentgenographic evidence of cardiac enlargement indicated that the inflammatory process had, in fact, been active. III. *Chronic overt rheumatic activity:* As representative of this group three patients were chosen of those in whom rheumatic heart disease was in a chronically active form, the continued activity being readily apparent. IV. *Single episodes of rheumatic fever:* This group consists of patients, selected at random, who experienced single acute episodes of rheumatic fever with carditis, each episode being followed by a prolonged and readily recognizable period of inactivity of the rheumatic process.

Criteria of Rheumatic Activity. The diagnosis of rheumatic fever during the initial period of hospitalization was unequivocal in all the patients under consideration, since all demonstrated overt evidence of rheumatic carditis in the form of characteristic cardiac murmurs of the organic type. Almost all of them had, in addition, evidence of cardiac enlargement, rheumatic pericarditis or congestive heart failure. In the case of out-patients, decisions concerning the degree of activity of the rheumatic process were made on conventional bases, e.g., changes in heart sounds and murmurs, electrocardiographic abnormalities, changes in heart size, the presence or absence of congestive heart failure and the stability of cardiac rate and rhythm. In the course of observation of these patients specimens of blood were routinely obtained for the determination of the erythrocyte sedimentation rate (ESR). Following centrifugation for the determination of the relative packed erythrocyte volume and corresponding correction of the ESR, the supernatant plasma was withdrawn and frozen. For the other tests made in this study such frozen specimens of plasma were thawed and the precipitated fibrinogen removed by centrifugation. Alternatively, calcium salts were added to cause coagulation of the plasma.

Laboratory Tests. Acute Phase Reactants. Erythrocyte sedimentation rate (ESR): The ESR was determined by a modification of the method of Rourke and Ernstene [*4*], as follows: Citrated venous blood (the blood minimally diluted by the addition of 2 to 3 per cent by volume of a 35 per cent solution of sodium citrate) was placed in a tall narrow tube, the column of blood being about 100 mm. in height. The height of the erythrocyte column relative to a fixed point on the tube was recorded at 5 minute intervals, and differences between such successive readings were noted. For computation of the crude ESR only those readings which fell approximately in an arithmetic progression were used, thus eliminating the decelerating effects due to the time required for rouleaux-formation at the beginning, and to the packing of erythrocytes at the end of the period. In this way several mutually corroborative observations of the rate of free fall of the rouleaux were available. Correction for variations in the volume percentage of packed erythrocytes was made by centrifugation of the tubes at 2,000 r.p.m. for fifteen minutes, determining the percentage of packed erythrocytes, and correcting to a value corresponding to 45 per cent volume of packed erythrocytes by the use of a nomogram developed by Ordway and Singer [*5*].

C-reactive protein (CRP): The CRP determination was carried out by superimposing a column of the serum to be tested and a column of rabbit anti-CRP serum in a capillary tube, as described by Anderson and McCarty [*6*]. After two hours of incubation at 37°C. and over-night incubation in the refrigerator the height of the precipitate was recorded to the nearest half millimeter. Each tube was accompanied by a control tube containing the serum to be tested and saline solution. Other controls in each test were those of anti-CRP serum and saline solution, and anti-CRP serum and a known positive control.

Serum mucoproteins: Serum mucoprotein tyrosine (MPT) was determined by a modification of the procedure described by Winzler [*7*], as follows: .05 ml. of serum was transferred by a Lang-Levy pipet to a plastic centrifuge tube. Nine ml. of saline solution were added and, after mixing these, 10 ml. of 0.39M sulfosalicylic acid solution. After fifteen minutes the tubes were centrifuged for fifteen minutes at 5,000 r.p.m. The resulting supernates were decanted through coarse filter paper. Of each supernate two or three 5 ml. portions were placed in test tubes and to each was added 5 ml. of a 1.67 per cent solution of phosphotungstic acid in 2N HCl. The tubes were stoppered and inverted several times immediately. After fifteen minutes all tubes were centrifuged for fifteen minutes at 2,000 r.p.m. The supernatant fluid was discarded and the tube drained. The precipitates were washed once in 5 ml. of 0.83 per cent phosphotungstic acid in 2N HCl, and to each washed precipitate was added 6 ml. of N/3 NaOH. (Blanks and bovine serum albumin standards were included at this point.) All tubes were placed in a boiling water bath for ten minutes, and after being cooled, 2 ml. of Folin's solution 1:3 were added to each. After mixing, the tubes were kept at room temperature for

twenty minutes and then read in a Klett colorimeter with a No. 66 filter. The resulting values were converted to MPT by a tyrosine standard. Early series of determinations were carried out on triplicate portions of the sulfosalicylic acid supernate but the values within these triplicates were in such close agreement that duplicates were used thereafter. In addition to the albumin control each test included at least one serum specimen in common with the preceding test.

In the case of both the CRP and MPT tests the validity of data obtained with frozen and stored specimens and plasma was verified by testing serum specimens freshly obtained from certain patients, and later specimens of plasma frozen and stored for periods up to several months. Further, among the highest CRP values obtained were those of acute phase serums which had been stored for a period of several years.

Streptococcal Serologic Tests. Streptococcal antihemolysin O (antistreptolysin, ASO) titers were determined with modifications of the method described by Todd [8], by incubation of 0.4 ml. volumes of serial twofold dilutions of serum with a 0.2 ml. of a solution of a lyophilized concentrate of streptococcal culture supernate, the 0.2 ml. containing 2.5 units of hemolysin under the conditions of the test, and 2 mg. of $Na_2S_2O_3$. After fifteen minutes of incubation at room temperature, 0.2 ml. of an 8 per cent suspension of sheep erythrocytes was added, followed by incubation for one hour at 37°c. and overnight in the refrigerator. The endpoint was taken as the last dilution of serum which prevented any hemolysis by the enzyme.

Streptococcal antihyaluronidase (AH): Titrations were performed by the mucin-clot prevention test, with neutralization of 3 units of the enzyme, as described elsewhere [9].

RESULTS

Unsuspected Activity of the Rheumatic Process. Clinical evidence of renewed activity of rheumatic fever during apparent quiescence of the disease was obtained in the following four cases:

Case I. J. I., a white Italian boy, had severe rheumatic carditis with congestive failure at the age of six years. After prolonged convalescence, a soft apical systolic blowing murmur of mitral insufficiency persisted for two years and finally disappeared completely. At the age of eight years, in the course of a routine clinic visit, the typical early diastolic high-pitched murmur of aortic insufficiency was heard to the left of the midsternum. The patient was on a regimen of sulfadiazine prophylaxis at this time, and examination two months prior had revealed no diastolic murmur. The pulse rate was 80 per minute, the sedimentation rate 10 mm./hour corrected, and the white blood count 9,500 per cu. mm. The patient was put to bed temporarily. The parasternal diastolic murmur persisted but no other evidence of rheumatic activity was detectable. The patient was gradually returned to full physical activity and did well until the age of ten years, when he experienced an overt episode of acute rheumatic fever with carditis. During this episode the apical systolic murmur of mitral insufficiency reappeared, and there was accentuation of the aortic diastolic murmur. During the next two years the apical systolic murmur was intermittently heard and then disappeared again. At the age of fourteen years the aortic diastolic murmur was still present.

Case II. V. S., a four and a half year old Negro girl, was convalescing from her initial episode of rheumatic fever with carditis when a typical clinical picture of Sydenham's chorea developed. A high-pitched apical systolic blowing murmur of rheumatic mitral insufficiency persisted following this illness. At the age of ten years, shortly after an episode of pertussis, an early diastolic blowing murmur to the left of the sternum was also noted for the first time. No diastolic murmurs had been detected on examination one month earlier. The pulse rate at this clinic visit was 78 per minute, the sedimentation rate was 30 mm./hour, corrected. There were no other signs or symptoms to suggest rheumatic reactivation. The sedimentation rate was repeated at intervals during the next several months and showed no change. Because the patient was at this time an obese adolescent female and there were no abnormal findings other than the slightly elevated sedimentation rate, she was returned to full physical activity. Oral penicillin prophylaxis had been maintained throughout this interval. No further evidences of rheumatic reactivation have appeared. The aortic diastolic murmur has persisted for three years to the present time; the apical systolic murmur has diminished in intensity and is heard only intermittently.

Case III. R. L., a Negro boy, experienced his initial attack of rheumatic fever at the age of five years. After eighteen months of convalescence he was returned to full physical activity. There was evidence of residual cardiac damage in the form of a loud, early diastolic blow to the left of the midsternum, indicating aortic insufficiency. Eight years later, at the age of fourteen, in the course of a routine clinic visit, a harsh, low pitched, short, systolic murmur was audible in the second right interspace, transmitted to the vessels of the neck, associated with a systolic thrill in the right supraclavicular and suprasternal areas. At the preceding examination three months earlier this murmur was not found. The patient had been entirely asymptomatic and free of any evidence of rheumatic activity during the nine years which followed his initial rheumatic attack and prior to the discovery of the murmur of aortic stenosis. At the time of discovery of the new murmur the sedimentation rate was 10 mm./hour, corrected; the electrocardiogram showed evidence of left ventricular hypertrophy; and

TABLE I

LEVELS OF THREE ACUTE PHASE REACTANTS (APR) AND OF ANTIBODIES TO TWO STREPTOCOCCAL ANTIGENS AT THE TIME OF OBSERVATION OF A NEW CARDIAC MURMUR IN PATIENTS WITH APPARENTLY INACTIVE RHEUMATIC HEART DISEASE

Patient	Time of Appearance of New Cardiac Murmur; Months After		Value of APR at Time of Observation of New Murmur			Streptococcal Antibody Titers at the Same Time	
	Beginning of Previous Episode (mo.)	Return of APR to Normal Values (mo.)	ESR (mm./hr.)	CRP (mm. precipitate)	MPT (mg./100 cc.)	AH	ASO
E. F.	58	54	8	0	3.9	48	96
J. I.	25	13	11	0	3.1	96	256
R. L.	94	84	9	0	3.4	48	128
V. S.	66	52	6	0	2.6	24	64

the orthodiagram revealed a slight increase in the size of the heart as compared to a similar study made two years earlier. The aortic diastolic murmur persisted throughout. The patient has been followed up for four more years subsequent to the discovery of the murmur of aortic stenosis. He had received no prophylactic medication. He has had no new manifestations of rheumatic activity or any evidence of cardiac failure.

CASE IV. E. F., a white girl, suffered her initial attack of rheumatic fever at the age of eight years. Transient and mild evidence of cardiac involvement was present at this time but subsequently disappeared completely. During the next five years systematic observations revealed no overt evidence of active rheumatic fever. No prophylaxis was administered during this interval. At a routine clinic visit at the age of thirteen years a definite high-pitched apical systolic blow of short duration was heard. The ESR was 8 mm./hour, corrected. Because there were no other symptoms noted in connection with this change in cardiac auscultation, no drastic restriction of physical activity was imposed. The murmur was heard at most clinic visits during the next eighteen months of observation. At the time of discharge from the clinic, at the age of fourteen years, the electrocardiogram was normal, size of the heart on x-ray was within normal limits, and the apical systolic murmur was still present.

The levels of three acute phase reactants and of two streptococcal antibodies were determined in serial serum specimens obtained from each of these four children. The results obtained in the serum specimens at the time the new manifestation of rheumatic heart disease was observed are shown in Table I. In this table it can be seen that the values of the erythrocyte sedimentation rate were in the range between 6 and 11, the C-reactive protein was in all cases negative, the serum mucoprotein tyrosine values were in the range 2.6 to 3.9 mg. per cent, the titers of streptococcal anti-hyaluronidase were between 24 and 48, and those of antistreptolysin between 64 and 256.

The courses of three patients in this group are charted in Figure 1. (In the case of the fourth, E. F., serums had been obtained only occasionally.) These charts extend from the beginning of the previous episode of acute rheumatic fever through the time of the observation of the new cardiac murmur. They show the states of activity of the rheumatic process, as judged by the criteria previously listed, the time of observation of the new sign of rheumatic involvement, and the results of serial determinations of the laboratory tests indicated in Table I.

The levels of the three acute phase reactants studied were plotted on the same coordinate axis. The choice of a common baseline for the three tests was complicated by the fact that in two of these tests (ESR and MPT) there is a relatively wide range of values in the normal population. In plotting the results of these two tests, therefore the baseline was taken as the lowest values encountered in the normal population (as well as in the population of subjects with inactive rheumatic infection) for reasons which will be discussed. In the case of the CRP the baseline value was taken as zero, since this

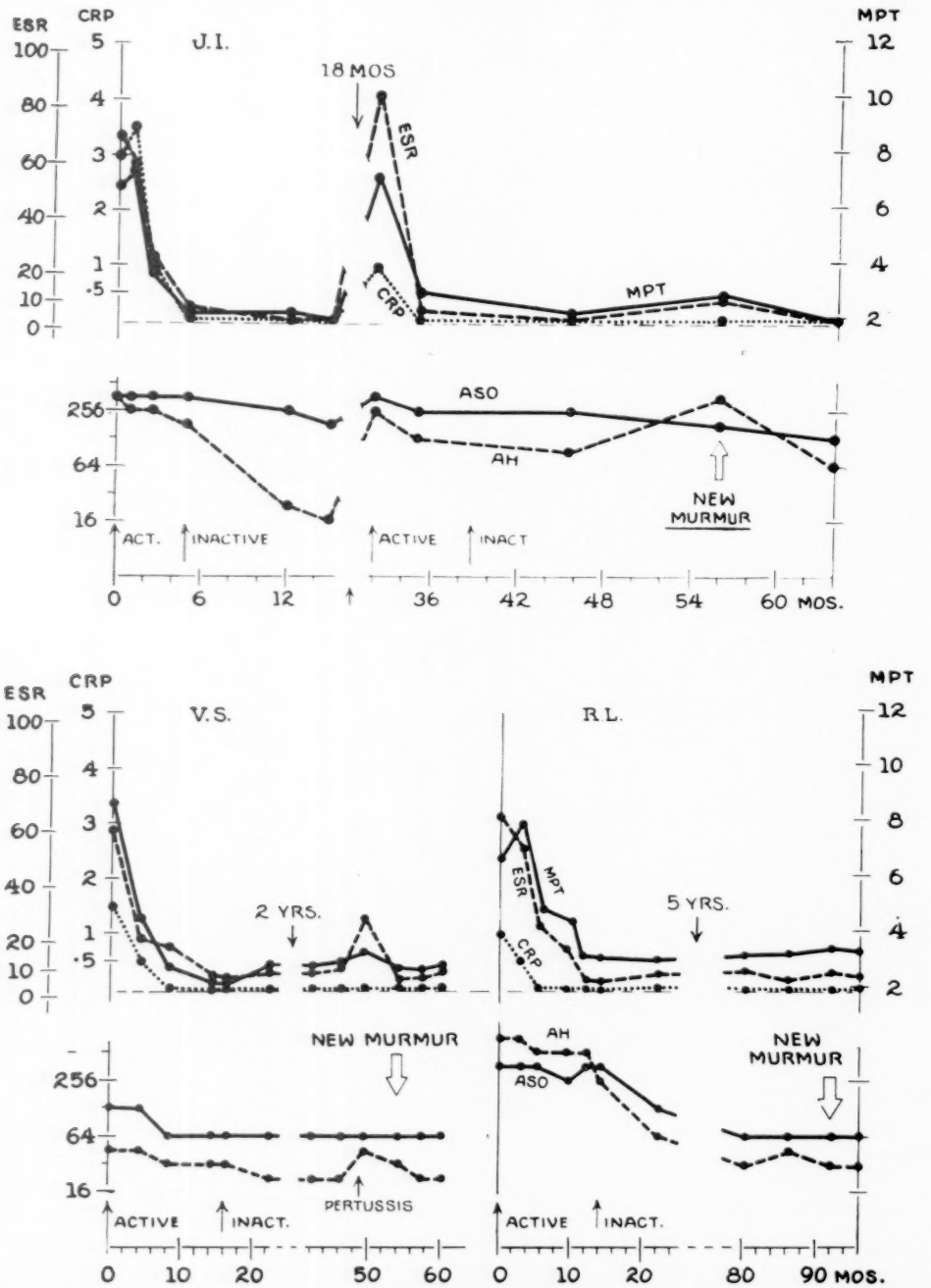


FIG. 1. Values of tests for three acute phase reactants, erythrocyte sedimentation rate (ESR, in mm. of free fall per hour, corrected to 45 per cent packed erythrocyte volume), C-reactive protein (CRP, in mm. of precipitate versus rabbit anti-CRP serum), mucoprotein tyrosine (MPT, in mg. per 100 cc. of serum), and titers of two antibodies to streptococcal antigens, anti-hemolysin O (antistreptolysin O, ASO) and antihyaluronidase (AH) in serums of three patients, from the beginning of a preceding episode of acute rheumatic fever until the time of observation of a new cardiac murmur.

value constitutes the normal range, all positive values being abnormal.

On examination of Figure 1 it is seen that the values of the acute phase reactants tested decreased at a rate usually found in uneventful convalescence to a plateau level within the normal range of values. These levels then remained in a normal range, with minor variations (except for the ESR during pertussis in V. S.), until the time of the observation of the extension of the rheumatic process, and beyond. In the case of J. I. the decrease in levels of acute

phase reactants was at as rapid a rate, and to as low a level, after the second episode as after the first.

The streptococcal serologic titers show the usual gradual decrease from their maximum values at the beginning of an episode of rheumatic fever.

Doubtful Rheumatic Activity. This group comprises two children in whom there was some uncertainty as to the activity of the rheumatic process but in whom the finding of progressive cardiac enlargement gave definite indication, in retrospect, of low grade activity of the rheumatic process.

CASE V. J. E., a white boy, had a streptococcal infection followed by severe rheumatic carditis at the age of four years. His initial hospitalization lasted fourteen months and was followed by bed rest at home for several more months. Approximately a year and a half after discharge he was considered well enough to be allowed to attend school. At this time a loud systolic blowing murmur was audible over the entire chest and a short mid-diastolic murmur was also present at the apex. The ESR was normal, as was the blood count. An x-ray taken approximately one year later showed a marked increase in heart size. The ESR was persistently less than 5 mm./hour. An electrocardiogram at this time showed right ventricular preponderance with wide notched P waves, indicating probable left auricular enlargement. The marked difference in cardiac size was taken as evidence of chronic activity of rheumatic fever. The patient continued to show evidence of low-grade rheumatic carditis, with the subsequent development of further cardiac enlargement, auricular fibrillation and chronic congestive failure. The sedimentation rate and antistreptococcal antibody titers have remained low during the seven years that have passed since his initial rheumatic episode.

CASE VI. B. D., a Negro girl, experienced her initial attack of rheumatic fever with carditis at the age of three and a half years. After a nine month period of complete bed rest she was allowed to walk, only to be rehospitalized three months later with fever, epistaxis and severe anemia. A short course of cortisone therapy at this time produced only a temporary suppressive effect on the rheumatic process. After ten more months of hospitalization the rheumatic process was considered to be inactive. A third hospitalization occurred at the age of five and a half years because of severe epistaxis and anemia. There was indecision as to the patient's state of rheumatic activity. However, at this time a roentgenogram of the thorax showed definite increase in cardiac size. Because of this indication of rheumatic activity, further bed rest was advised. Subsequently the patient had several more episodes of epistaxis which required transfusions. In retrospect, this patient had chronic rheumatic activity from age three and a half to six years. At present the patient is eleven years old and for the past three years the rheumatic process has been considered to be entirely inactive. She is allowed full activity and is leading an almost normal life, despite the presence of some residual cardiac damage.

The clinical courses and results of the laboratory studies of these two patients are shown in Figure 2. In this figure it can be seen that the values of all the acute phase reactants measured and of both streptococcal antibodies were within normal limits at the time cardiac enlargement was observed. In the case of B. D. it can be seen that the values of the acute phase reactants fell at least as rapidly after the second acute episode as after the first, and reached levels as low as after the first episode. In the case of J. E. it is of interest that the levels of these three acute phase reactants were not elevated even in the presence of a grade of inflammation sufficient to produce a series of severe clinical manifestations: further cardiac enlargement, auricular fibrillation, cardiac decompensation. These manifestations occurred within the year which is included in the figure following the observation of cardiac enlargement.

Overt Chronic Activity of the Rheumatic Process. In contrast to the subclinical or borderline activity of rheumatic infection, which is often of such low grade as to be detected only in retrospect, is the situation of chronic activity of a degree which produces continuous clinical evidence of such activity for a period of months or years. A very brief summary of three such cases follows:

CASE VII. D. S., a Negro girl, was first observed at the age of six and a half years with definite evidence of rheumatic heart disease and mild congestive heart failure. Three months of hospitalization with subsidence of the congestive heart failure was followed by one year of bed rest and convalescent care. Attempts to restore her to physical activity were associated with recurrence of congestive heart failure, and rehospitalization was required. A second year of convalescent care resulted only in progression of the cardiac involvement and the development of episodes of congestive failure which required further hospitalization at The Children's Hospital of Philadelphia. The patient received two courses of hormone therapy but cardiac enlargement and heart failure continued. The situation was finally considered to be

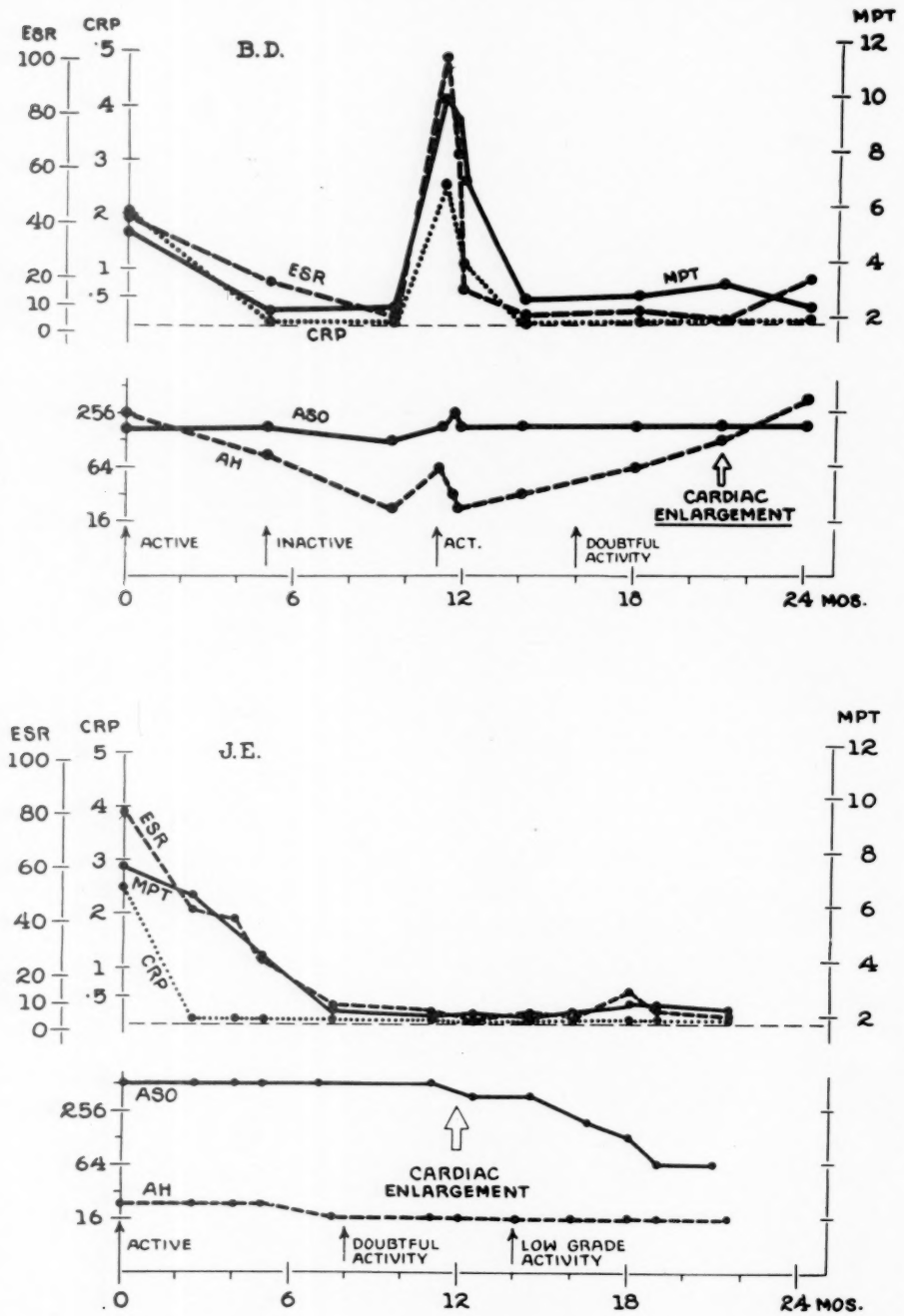


FIG. 2. Levels of three acute phase reactants and two streptococcal antibodies in two patients in whom cardiac enlargement was observed at a time when activity of rheumatic fever was in doubt.

hopeless and the patient was discharged to bed rest at home. Examination at subsequent clinic visits has indicated progressive cardiac involvement with massive cardiac enlargement, very loud apical systolic and presystolic murmurs and a parasternal aortic diastolic murmur.

CASE VIII. D. A., a Negro boy, was hospitalized for acute glomerulonephritis at the age of nine years. At this time a short apical systolic blowing murmur and a parasternal aortic diastolic murmur were discovered. After twenty-four months of convalescent care, the apical systolic murmur disappeared, the ESR fell to the normal range, and the physical findings remained stable. At the age of fourteen, while the patient was taking penicillin prophylaxis only sporadically, there was a definite recurrence of rheumatic fever, with carditis which persisted until

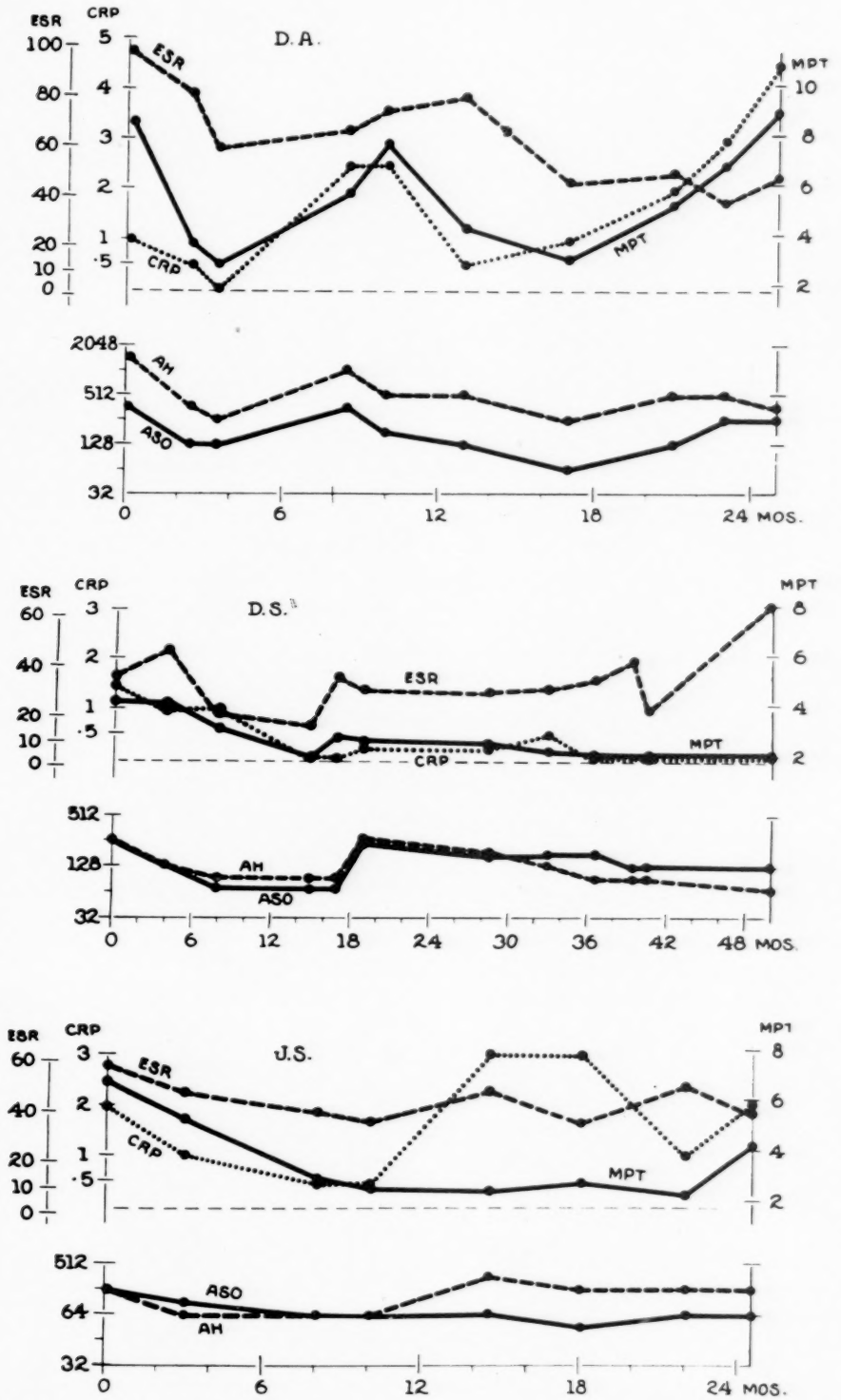


FIG. 3. Values of three acute phase reactants and the two streptococcal antibodies in three patients in whom there was chronic activity of rheumatic fever at a clinically recognizable level.

death. The patient had been hospitalized during most of this period, and three courses of treatment with cortisone or ACTH did not appear to alter the downhill course of the disease. During the terminal illness the physical findings included the murmurs of mitral insufficiency and aortic insufficiency, massive cardiac enlargement, auricular fibrillation and profound congestive failure.

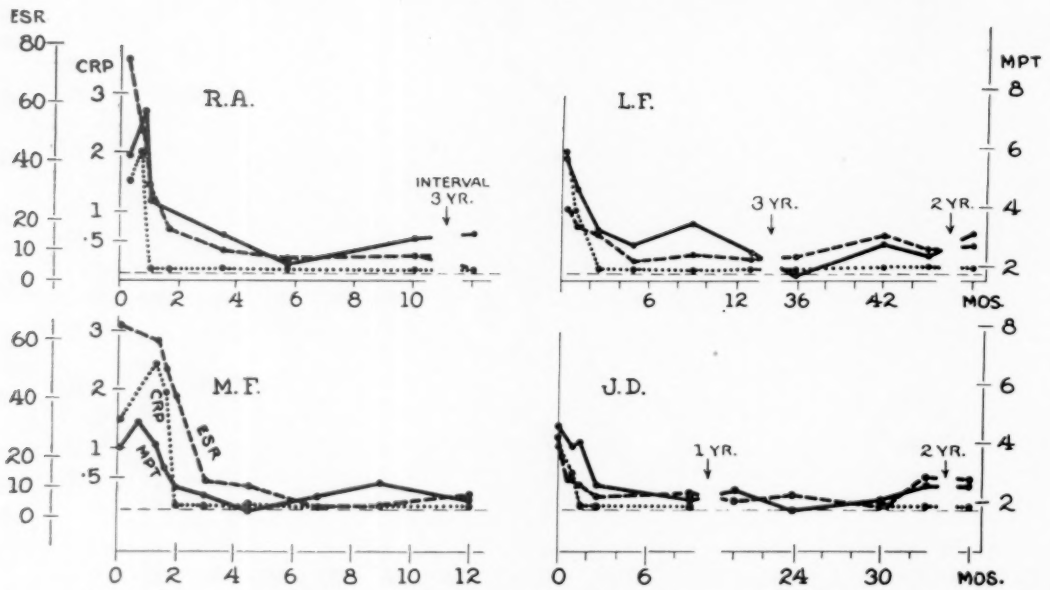


FIG. 4. Values of the three acute phase reactants during and after single acute episodes of rheumatic fever which were not followed by evidence of extension of the rheumatic process during the period of quiescence.

CASE IX. J. S., a Negro boy, was first hospitalized at the age of twelve years with active rheumatic carditis and mild congestive heart failure. A fourteen month period of bed rest did not result in subsidence of the rheumatic activity. After this interval his condition worsened and his return from a convalescent institution to a general pediatric hospital was necessary. Congestive failure was more severe and associated with an episode of acute rheumatic pericarditis. Seven months of hospitalization were followed by a short trial of home care and finally a return to hospital care because of aggravation of the congestive heart failure. The patient died four months later with congestive heart failure, mitral insufficiency and mitral stenosis.

The results of the three acute phase tests and two streptococcal antibody titrations on serial specimens of serum from these patients are shown in Figure 3. In this figure it can be seen that the levels of all the acute phase reactants were elevated during prolonged periods in all these children, and that at any time one or more of those reactants were quite far from the normal range. The streptococcal serologic titers showed no major variations in titer but remained in the same general range throughout the period of observation.

Single Episodes of Rheumatic Fever Followed by Rheumatic Inactivity. Another group of patients in whom the levels of these acute phase reactants were studied for comparison is one in which a single episode of rheumatic fever is followed by apparent quiescence, with no evidence of further involvement for a period of years. The levels of the same three acute phase reactants, as observed in four such patients over periods up to six years, are charted in Figure 4. These patients were not treated with adrenal hormones. The pattern of decline in these levels is typical of uncomplicated rheumatic fever, and is similar to that seen in Figure 1. On examination of those portions of the charts which follow the point at which time the rheumatic infection was considered entirely inactive, variations as high as 1.2 mg. per cent of MPT can be found within a given patient, and differences in ESR as great as 10 mm./hour. Such variations were not followed by evidence of extension of the rheumatic process either during the period charted (two to three years in three of these patients), or since then (one to three years in the four patients). Similar ranges in variation of the ESR and MPT were found in the quiescent stages of rheumatic fever in other patients in this group who were not included in Figure 3.

COMMENTS

Laboratory Tests Included in This Study. Although the five laboratory tests reported in the table and figures were applied to this study because they can give evidence of activity of rheumatic fever, these tests belong to two distinct groups, one for the estimation of acute phase reactants, the other for relative measure-

ment of antibodies to streptococcal antigens. These two groups of tests differ qualitatively in their relationship to this disease. "Acute phase reactant" is a term which has been applied to a growing number of recognized constituents of serum which are present only, or in increased concentration, during the active phase of a number of diseases. These diseases are of many kinds, and appear to have as their sole common characteristic the destruction of tissue, whether because of a protracted inflammatory process, infarction or malignancy. The acute phase reactants are, then, entirely non-specific to rheumatic fever. In fact, each of the three tests in this group made routinely in this study was first described in connection with some other disease. In addition to the ESR, CRP and MPT this group includes tests for the concentration in serum of non-specific hyaluronidase inhibitor [*10*], hexosamine [*11*], non-glucosamine polysaccharide [*12*], complement [*13*], and others. Of this list the ESR, CRP and MPT tests were included in this study because they are, in decreasing order as named, the ones which have been most widely used in assessing the degree of activity of the inflammatory process in rheumatic fever.

The streptococcal serologic tests also are not specific for rheumatic fever, since it is quite unlikely that any of the streptococcal antigens to which relative estimations of antibodies have been made in such tests is a specific pathogenetic agent of this disease. However, these tests have some relationship to rheumatic fever in that they involve antigens from an organism, the hemolytic streptococcus, which has often been found in epidemiologic [*14*] and bacteriologic [*15,16*] association with this disease. Moreover, frequency distributions of titers of a number of antibodies to streptococcal antigens have been found to be quite similar in groups of patients with acute rheumatic fever and groups of convalescents from acute streptococcal infection [*17–19*]. Of a number of streptococcal serologic tests which have been described the two which were chosen for this study are the ASO, because of its wide use, and the AH because the titer of this antibody has been found to change somewhat more readily with gross changes in activity of rheumatic fever [*20*] and to have a frequency distribution of titers which extends appreciably higher in acute rheumatic fever than in convalescence from streptococcal infection [*20,21*].

In the acute phase reactants, the choice of a common baseline for the most useful comparison of levels within this group presented a problem, since in two of these tests there is an appreciable range of values found in the presumably normal population (and in subjects with quiescent rheumatic fever). Ranges of values of the ESR for apparently normal subjects have been reported in the literature to be as low as 3 mm./hour [*22*] and as high as 24 mm./hour [*4*] (the latter even after correction for relative volume of packed erythrocytes) and of the MPT in normal children from 1.5 to 4.5 mg. per cent [*23,24*]. Under these circumstances it would not appear to be justifiable to regard a convalescent from rheumatic fever as having attained a normal ESR when the value of that test reaches 20 mm./hour, since the normal value for that subject is not, in general, known. Rather, we have considered that the ESR ceases to give evidence of continued rheumatic activity when its value falls to a plateau level, and the same consideration would appear to apply to the MPT value. For greater usefulness of these graphs, then, the common baseline for the acute phase reactants was set at 3 mm./hour for the ESR, 1.8 mg. per cent for the MPT, with no mark at the upper limit of the respective distributions in the normal population as a whole, and at 0 in the case of the CRP.

The Persistence of Rheumatic Fever at a Subclinical Level. The clinical and laboratory observations made in the first four patients described here (group 1) indicate that the rheumatic process can occur or continue during what is considered the quiescent phase of the disease, and at a level of activity sufficient to produce clinical evidence of extension of the process in the form of a new cardiac murmur, but too low to give any other overt manifestations. Since this clinical evidence is based on an auscultatory finding, i.e., a cardiac murmur, it should be noted that these patients were examined by one or more of the permanent members of the respective Rheumatic Fever Clinics at each visit. In each of these four children the murmur in question was not observed during any of the numerous clinic visits during the period indicated in Table 1, and was then noted during the clinic visits of a number of years thereafter.

Since the observation of a new cardiac murmur of valvular insufficiency constitutes the evidence for rheumatic activity in these patients, the possibility should be mentioned that valvular insufficiency might be explained on

the basis of scarring of tissues formerly the site of inflammation, rather than from a current inflammatory process. However, this is quite a remote possibility, especially in the group of patients presented here, since there had been so long an interval of time since the rheumatic process was last considered active (thirteen to eighty-five months), as can be seen in the table.

Serial examinations of the acute phase reactants in the patients of this group yielded results entirely different from those found in patients with overt, continued activity of the disease. Of the three acute phase reactants measured, the levels fell in patients of group I at about the same rate, and to as low a range of levels, after the episodes described here as in uncomplicated convalescence from rheumatic fever in other patients chosen at random, such as those included in Figure 4.

Again, although minor variations in the levels of these acute phase reactants were found, and occasionally these represented increases at the time of the new clinical finding, all such variations were within the range of variations of such levels which could be found in children with no subsequent clinical evidence of extension of the rheumatic process over a period of several years of periodic observation, as can be seen in Figure 4. The data obtained in the two patients of group II indicate that values of these three acute phase reactance in the normal range can be found even in cases of doubtful or borderline activity of rheumatic fever.

The Relation of These Observations to Other Data on Long-term Activity of the Rheumatic Process. Recent pathologic observations made on auricular appendages removed at the time of mitral commissurotomy have indicated a rather surprisingly frequent finding of Aschoff bodies in patients presumed to be inactive. Under the generally accepted interpretation of the Aschoff body these would indicate activity of the rheumatic process, in this case probably of very low grade and long duration, although the degree of rheumatic activity implied by a number of the Aschoff bodies found in such situation has been questioned in one recent study [*25*]. The clinical situation described in the present paper offers evidence of an intermediate range of subclinical rheumatic activity, between this situation and that of overt chronic activity of rheumatic fever. It is, then, likely that a fairly continuous range of severity of long-term activity of the rheumatic process can exist. In descending order of severity these would include: first, overt chronic activity, from that with fatal termination through de-decreasing order of severity; next, the non-overt chronic or episodic activity described here (the rare finding of classic signs of mitral stenosis in subjects with no known history of rheumatic fever and with no evidence of congenital heart disease might constitute another example of rheumatic activity at this level); then, perhaps, a level reflected in the increased susceptibility to rheumatic fever of subjects with a past history of this disease, in comparison with the normal population; and finally, the level of activity represented by the incidental histologic finding of Aschoff bodies, with its own range of decreasing degrees of involvement.

Two recent reports are of interest in connection with the observations reported here, and with the range of possible degrees of activity of the rheumatic process indicated above. In one of these Elster and Wood [*26*] reported the absence of CRP in the serum of patients whose auricular appendages, removed at mitral commissurotomy, were found to contain Aschoff bodies. In the other study Weinstein, Boyer and Goldfield [*27*] reported on a group of subjects who had had scarlet fever seven years previously. Of 110 such patients ten had, at the conclusion of the scarlet fever, given evidence of prolonged auriculoventricular conduction time in the electrocardiogram but had not satisfied the usual criteria for the diagnosis of rheumatic fever, nor did they give any history of rheumatic fever in the intervening seven years. Of this group of ten, six were found to have a clearly recognizable cardiac murmur characteristic of rheumatic heart disease when re-examined seven years later.

A comment should be made on the relation of antibiotic prophylaxis of rheumatic fever to subclinical activity of the disease. If such a grade of activity can begin *de novo*, in a subject in whom the rheumatic process has become truly inactive, then one might expect the frequency of the phenomenon to be sharply reduced by the current regimens of rheumatic prophylaxis, as has been observed in the case of acute episodes of the disease. On the other hand, subclinical activity which is continued directly from an acute episode of rheumatic fever would probably not be affected by such a prophylactic regimen, since episodes of rheumatic fever can not be terminated by this procedure. Two of the four patients with truly unsuspected rheumatic fever

presented herein (group 1) had been maintained on a regimen of such prophylaxis.

Correlation of Values Among the Acute Phase Reactants Studied. The results obtained in the serial examinations for the three acute phase reactants in the serums of the three types of patients with rheumatic fever indicate that the levels of these three reactants are not necessarily correlated with each other. At the extreme ranges of activity studied there was general agreement among the values of these tests, at the onset of episodes of rheumatic fever of at least a moderate degree of severity the values of all three reactants were almost always elevated, and at the state of subclinical activity all three tests yielded values so low as to give no indication of the persistence of the inflammatory process. At intermediate levels of activity, however, the data obtained in the patients represented in the figures, and in other patients, often showed a substantial lack of correlation so that, for example, two of the three tests might suggest a moderate degree of activity and the third test a slight degree or a marked degree of activity; again, two of the tests might show excellent agreement with each other in relative values over a considerable period of time while the third showed substantial differences from the course of the first two. In the body of data collected in this study these two differences were found to occur in any of the three combinations possible among three tests. In this study such differences could most clearly be seen in patients with overt chronic rheumatic activity, such as those included in Figure 2. (Evidence of lack of correlation among values of these acute phase reactants, even in the acute stage of the disease, can be found in a recent report by Adams [*24*].) Also, in the convalescence from acute episodes of rheumatic fever no constant order of return to normal values of the three acute phase reactants was found. Most commonly the CRP returned to normal first, and the MPT and ESR appeared to be of fairly similar sensitivity, as was observed also by Kelley et al. [*23*], the MPT being the last to return to normal somewhat more often than was the ESR.

SUMMARY

In four children who had had rheumatic fever a new cardiac murmur was observed in the course of routine examination at a time when the disease had been regarded as in a quiescent stage. This was taken as evidence of activity of the rheumatic process. The values of three acute phase reactants (the erythrocyte sedimentation rate, C-reactive protein and serum mucoprotein) and of antibodies to two hemolytic streptococcal antigens (antistreptolysin and antihyaluronidase) were found to be within normal limits in these patients at the time the evidence of extension of the rheumatic process was observed, and to have shown only minor variations during the preceding months. The values of these three acute phase reactants were also within normal limits in two other patients in whom the activity of the rheumatic process was doubtful or at a barely detectable level. The results of serial determinations of these values are presented in some of these patients, as well as in a group with long continued overt activity of rheumatic fever, and of other patients in whom a single episode of this disease was followed by a prolonged quiescent period.

The significance of these findings in relation to variants in the natural history of rheumatic fever is discussed.

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The Accuracy of Diagnosis of Myocardial Infarction*

A Clinicopathologic Study

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THE clinical syndrome produced by myocardial infarction has been recognized for a comparatively short time, but even in 1919, within ten years of the first description of the dominant clinical features, Herrick [*14*] said with some confidence that " . . . these symptoms will often enable one to make a reasonably certain diagnosis of acute obstruction of the coronary artery." Since then, with the increasing incidence of the disease [*6,24,28*], and with the added awareness of clinicians of the manifold ways in which it may present, its recognition as a clinical entity has increased enormously. In the 1920's students rarely saw a case, and in 1923 only three cases were discovered in 471 autopsies performed at the Royal Infirmary, Edinburgh. And now, in the same hospital, still supporting the same number of medical beds, about 500 cases are diagnosed annually.

Accuracy in the diagnosis of myocardial infarction, apart from being academically desirable, is of considerable social, economic and medico-legal importance, not only to individuals but also to commercial and national institutions. It was therefore felt that a critical assessment of the present standards of clinical diagnosis of the condition, with and without electrocardiographic assistance, would be of value.

METHOD

In this hospital 1,646 postmortem examinations were made during the two-year period 1954–1955. All these cases were reviewed and patients suspected clinically of having had a recent myocardial infarct, or found at autopsy to have had one, were selected for the purposes of this study. No case was included in which only an old infarct was found at autopsy, unless a recent infarct had been suspected clinically; nor any in which the clinical history related only to old episodes. The records selected for particular attention were then divided into three groups: Group I: Patients in whom the clinical diagnosis of a myocardial infarct was substantiated at postmortem examination. Group II: Patients in whom the clinical diagnosis of myocardial infarction was not confirmed at autopsy. Group III: Patients coming to autopsy with a provisional diagnosis other than myocardial infarction but who were found to have had, although not always to have died from, a myocardial infarct.

From the central electrocardiographic files it was possible to trace the corresponding electrocardiograms, to check the electrocardiographic diagnosis made during life, and to correlate the interpretations with the autopsy findings. Twelve standard leads were recorded routinely, additional praecordial leads being occasionally employed if required.

During the period under study the hearts of nearly all the patients known to have had, or suspected of having had, a myocardial infarct were specially examined by pathologists with a particular interest in coronary artery disease, using either injection or serial slicing technics.

RESULTS

In 1954 and 1955 a total of 1,075 cases of myocardial infarction were diagnosed clinically in this hospital, and of these 247 patients died, giving a mortality rate of 24 per cent. A postmortem examination was performed in 214 of the fatal cases.

The findings in the various groups were as follows. (Table I.) Group I: Cases in which the clinical diagnosis of infarction was confirmed. There were fifty-seven cases in this group in 1954 and sixty-one in 1955, making a total of 118 cases. Group II: A clinical diagnosis of infarction without confirmation at postmortem. This group contained fifty-five cases in 1954 and forty-one cases in 1955, making a total of ninety-six cases.

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Group III: Cases in which myocardial infarcts, unsuspected clinically, were found at autopsy. There were twenty-nine such cases in 1954 and twenty-three in 1955, making a total of fifty-two cases.

These figures show that of the patients suspected clinically of having had infarcts (groups I and II). Almost as many were found not to have had infarcts as were found to have had them. A detailed analysis of the final pathologic diagnosis in every case in group II was therefore made. (Table II.) These final diagnoses could be divided into four main groups: cardiovascular diseases, pulmonary diseases, deaths associated with operations and a small group of miscellaneous diseases.

The patients with gross coronary atheroma, sometimes with occlusion but without infarction, and those with pulmonary emboli, accounted for almost one-third of the diagnostic errors. Pneumonia was the final diagnosis in thirteen cases. Peripheral shock was considerable in these patients and most of them died soon after admission.

Twelve patients died within a few hours of operation, usually having "collapsed" a varying time before death. Haemorrhage at the site of operation was often found but sometimes no precise cause for death was revealed, other than the operation itself. Forty-eight patients were sent to autopsy from surgical wards with a provisional diagnosis of myocardial infarction but an infarct was found in only thirteen instances. However, in eighteen additional cases from surgical wards myocardial infarcts were found when they had not been suspected clinically.

The provisional diagnoses with which the fifty-two patients in group III were sent to autopsy were also analysed. (Table III.) Patients with a diagnosis of congestive or left-sided heart failure formed the largest group. Those thought to have had pulmonary emboli were next in frequency, and this diagnosis was often made because of the suddenness of death. The four patients with extensive carcinomatosis also had myocardial infarcts. Similarly, the six patients dying from cerebrovascular accidents had both conditions simultaneously.

All patients dying shortly after admission, or before there was time to complete the necessary investigations, and all those dying unexpectedly, even though they had been in the ward for some

TABLE I
ANALYSIS OF CLINICAL DIAGNOSES COMPARED WITH POSTMORTEM FINDINGS

Group	Diagnosis	1954	1955	Total
I	Clinically: myocardial infarct	...	...	...
	Autopsy: myocardial infarct	57	61	118
II	Clinically: myocardial infarct	...	...	...
	Autopsy: other diagnosis	55	41	96
III	Clinically: other diagnosis	...	...	...
	Autopsy: myocardial infarct	29	23	52
	Total	141	125	266

TABLE II
FINAL DIAGNOSES IN PATIENTS SENT TO POSTMORTEM WITH QUESTION OF MYOCARDIAL INFARCT AND FOUND TO HAVE DIED FROM OTHER CAUSES

Final Diagnosis	1954	1955	Total
Cardiovascular:			
Pulmonary embolus	7	7	14
Gross coronary sclerosis (no infarction)	4	10	14
Congestive failure: pulmonary oedema	6	6	12
Aortic aneurysm, ruptured or dissecting	5	2	7
Pericarditis	4	2	6
Cor pulmonale	4	1	5
Mesenteric embolus	1	..	1
Aortic stenosis	1	..	1
Pulmonary:			
Pneumonia, pleural effusion	10	3	13
Atelectasis	..	2	2
Carcinoma	1	..	1
Associated with operations:			
Shock: bleeding	8	4	12
Fat embolism	..	1	1
Other conditions:			
Ruptured oesophageal varices	..	1	1
Ruptured gall bladder	..	1	1
Ruptured gastric ulcer	..	1	1
Disseminated lupus erythematosus	1	..	1
Meningovascular syphilis	1	..	1
Haemochromatosis: cancer of liver	1	..	1
Lymphosarcoma	1	..	1
Total	55	41	96

time, were classified as cases of sudden death. Many of these patients were sent to autopsy with a provisional diagnosis of myocardial infarction or pulmonary embolism.

In the two years under review there were 132 instances of sudden death (ninety-five patients from medical wards and thirty-seven from surgical wards) and seventy-four of these patients actually had myocardial infarcts at autopsy. In the seventy-four cases of sudden death from myocardial infarction, there was previous evidence of coronary artery disease in fifty-five cases. This took the form of a history of angina or of previous infarction, or else a previous electrocardiogram presented the pattern of infarction or of myocardial ischaemia.

TABLE III
PATIENTS SENT TO AUTOPSY WITH OTHER DIAGNOSIS AND FOUND TO HAVE HAD A MYOCARDIAL INFARCT

Clinical Diagnosis	1954	1955	Total
Congestive failure: left ventricular failure	9	6	15
Pneumonia	3	1	4
Pulmonary embolus	4	5	9
Extensive carcinoma	2	2	4
Uraemia	1	2	3
Cerebral haemorrhage	5	1	6
Postoperative shock	1	4	5
Bronchial carcinoma	2	..	2
Multiple emboli	1	1	2
Ruptured aortic aneurysm	1	..	1
Septic wound	..	1	1
Total	29	23	52

In the 132 cases of sudden death, fifty-three patients had previously had an electrocardiogram. In thirty-five instances a recent record indicated infarction, and in thirty-three of these, acute infarction was found at post-mortem. The two patients not showing pathologic evidence of recent infarction had electrocardiograms indicating old infarction. They had both collapsed and died in minutes some days after their last electrocardiogram was taken. In both cases there was a recent coronary occlusion and it was thought that insufficient time had elapsed between the onset of the attack and death for the pathologic changes of infarction to develop. Only one patient died suddenly of an infarct after having had a recent electrocardiogram which gave no evidence of this. The electrocardiogram which was taken six days before death showed only non-specific T wave changes, and at autopsy a very recent anterior infarct was found.

In 1954, in the 141 cases in all groups, sixty patients had had an electrocardiogram recorded shortly before death. A "recent" electrocardiogram was taken to mean one obtained not longer than a month before death, and preferably during the course of the final admission. In 1955, in fifty-six of the 125 cases a recent electrocardiogram had been taken. Thus in the 266 cases in all groups, 116 patients had had a recent electrocardiogram taken.

TABLE IV
ELECTROCARDIOGRAPHIC FINDINGS IN PATIENTS SUSPECTED CLINICALLY OF HAVING MYOCARDIAL INFARCTION

Year	Patients in Group I and II (No.)	Patients with Recent Electrocardiogram (No.)	Patients with Correct Electrocardiographic Diagnosis (No.)
1954	112	54	51
1955	102	43	40
Total	214	97	91

TABLE V
ANALYSIS OF "INCORRECT" ELECTROCARDIOGRAMS

Patient	Time of Electrocardiogram Before Death	Electrocardiographic Diagnosis	Pathologic Diagnosis
I	8 days	Abnormal: ? ischaemia	Recent apical infarct
II	2 days	Left bundle branch block	Recent apical infarct
III	Day of death	ST shifts: acute ischaemia	Subendocardial infarct
IV	Day of death	Left bundle branch block	Recent posterior infarct
V	Day of death	Left bundle branch block	Recent anterolateral infarct
VI	6 days	Abnormal: ? ischaemia	Subendocardial infarct

The patients in groups I and II were all sent to autopsy with a provisional diagnosis of myocardial infarction. Therefore the patients in these two groups might reasonably have been expected to have had their electrocardiogram recorded, if time permitted, in order to clarify the diagnosis. There were 214 patients in these two groups, ninety-seven of whom had recent electrocardiograms taken; so the majority of the

TABLE VI

ELECTROCARDIOGRAPHIC FINDINGS IN PATIENTS FOUND AT POSTMORTEM TO HAVE HAD A RECENT MYOCARDIAL INFARCT UNDIAGNOSED CLINICALLY

Patient	Clinical Diagnosis	Time of Electrocardiogram Before Death	Electrocardiographic Findings	Postmortem Findings
I	Congestive failure	4 days	Old anterior infarct	Recent apical infarct
II	Left-sided failure	4 days	? posterior damage	Recent posterior infarct
III	Congestive failure	10 days	? posterior damage	Recent posterior infarct
IV	Peripheral and pulmonary emboli	Day of death	Anteroseptal infarct	Recent anterior infarct
V	Carcinomatosis	1 month	Non-specific changes	Recent postlateral infarct
VI	Pulmonary embolus	5 days	Old posterior infarct	Recent anterior infarct
VII	Congestive failure; pulmonary infarct	2 days	Old posterior infarct	Recent posterior infarct
VIII	Cerebral hemorrhage	1 year	Non-specific changes	Recent anterior infarct
IX	Pneumonia	10 days	Digitalis effects	Recent posterior infarct
X	Congestive failure	6 days	Old anterior infarct	Recent (3 day) anterior infarct
XI	Congestive failure	2 days	Recent posterior ischaemia	Recent posterior infarct
XII	Pulmonary oedema	Day of death	Acute ischaemia	Recent posterior infarct
XIII	Congestive failure	5 days	Non-specific changes	Subendocardial infarct
XIV	Left-sided failure	12 days	Non-specific changes	Recent apical infarct
XV	Pulmonary embolus	6 weeks	Posterior infarct	Old and recent posterior infarct

116 patients with recent records were found in these two groups.

In correlating the electrocardiographic and autopsy findings, a correct electrocardiographic diagnosis was considered to be one which definitely indicated the myocardial damage later confirmed at autopsy. In some instances the precise localisation of the infarct was incorrectly made electrocardiographically; but when the electrocardiogram was reported as showing recent damage and such damage was found at autopsy then the report was regarded as "correct" for practical diagnostic purposes. Such a correct interpretation was made in ninety-one of the ninety-seven cases in which a recent electrocardiogram had been obtained. (Table IV.)

There were six "incorrectly" diagnosed cases. In three of these left bundle branch block was present and there were non-specific changes in the others, interpreted as possibly due to myocardial ischaemia. (Table V.) There was recent "through and through" infarction in the three patients with left bundle branch block, subendocardial damage in two of the others, and a recent apical infarct in the sixth, a patient who died eight days after the last electrocardiogram was obtained.

Fifteen patients in group III had had electrocardiograms taken at varying times before death. (Table VI.) In some patients the myocardial infarction obviously occurred after the last electrocardiogram had been obtained but in others an equivocal electrocardiographic report of possible myocardial damage was evidently not accepted by the clinician as sufficient support for a diagnosis of myocardial infarction.

Many patients in groups I and II who were believed to have sustained myocardial infarcts died suddenly before adequate investigations could be carried out, but the patients whose deaths were not sudden had all been in the wards for a sufficient time for investigations to be undertaken and a reasonably firm diagnosis made.

There were ninety-six patients who had non-sudden deaths in groups I and II, and only fifty-nine of these patients were found to have had infarcts. Fifty-nine of the ninety-six patients had had a recent electrocardiogram; but the patients who had electrocardiograms were not necessarily the ones in whom infarcts were found at autopsy. In 1955, twenty-seven patients with non-sudden deaths had infarcts proved at autopsy; but thirty-two patients had electrocardiograms, some of them dying from causes other than myocardial infarction.

There were twenty-three patients in 1954 and fourteen in 1955 who were diagnosed by clinical methods alone as having died from myocardial infarction. They did not die suddenly and yet no electrocardiograms were taken to substantiate the clinical impression. Only thirteen of these thirty-seven patients actually had myocardial infarcts, while twenty-four did not. Thus, without availing himself of electrocardiographic help, the clinician was correct in his diagnosis of infarction in only one-third of these cases. The final diagnoses in these patients who did not have myocardial infarcts, although clinically thought to have had them, are given in Table VII.

TABLE VII

FINAL DIAGNOSIS IN TWENTY-FOUR PATIENTS NOT DYING SUDDENLY AND DIAGNOSED AS HAVING MYOCARDIAL INFARCTS WITHOUT ELECTROCARDIOGRAPHIC CONFIRMATION

Postmortem Number	Final Diagnosis
192/54	Calcified pericardium
198/54	Coronary sclerosis: myocardial fibrosis
275/54	Uraemic pericarditis
281/54	Malignant prostate (known): bronchopneumonia
293/54	Bronchopneumonia: pleural effusion
341/54	Coronary sclerosis: myocardial fibrosis
367/54	Miliary tuberculosis: pulmonary oedema
472/54	Coronary sclerosis: myocardial fibrosis
505/54	Haemochromatosis: portal vein thrombosis
542/54	Postoperative aspiration of vomit
644/54	Mitral stenosis: mesenteric embolus
665/54	Lobar pneumonia: pleural effusion
712/54	Hypertension: congestive failure
5/55	Dissecting aortic aneurysm
87/55	Aortic regurgitation, rheumatic
138/55	Coronary sclerosis: cerebral haemorrhage
213/55	Pulmonary embolism
247/55	Acute pericarditis
289/55	Fat embolism
436/55	Cerebral infarction: pulmonary thrombosis
741/55	Ruptured oesophageal varices
760/55	Postcholecystectomy haemorrhage
801/55	Coronary sclerosis: myocardial fibrosis
844/55	Pulmonary embolus

COMMENTS

Any investigation based on random postmortem examination reports necessarily has inherent faults [*20*]. The group studied is selected, and in this series some of the patients were sent to autopsy either because the clinician responsible for their care in life was particularly interested in coronary artery disease or because there was sufficient doubt about the diagnosis to warrant autopsy for clarification. However, since 86 per cent of the patients dying in the hospital of myocardial infarction were autopsied, a fair sample was probably obtained.

Baer and Frankel [*1,2*] in an extensive study of cases of myocardial infarction over a twenty-one year period selected for detailed analysis 378 case records (of 508 in their hospital files) in which the final diagnosis had been myocardial infarction. In the remaining 130 cases there was insufficient clinical, electrocardiographic or pathologic evidence on which an unequivocal diagnosis of myocardial infarction could be based. Thus, in 130 of 508 cases a clinical diagnosis of myocardial infarction was made, apparently without conclusive evidence. Meakins [*22*] and Wood [*29*] both believed that the diagnosis of myocardial infarction was made too frequently. However, Yater et al. [*31*] in a pathologic study of myocardial infarction in young soldiers, aged eighteen to thirty-nine, found a diagnosis accuracy rate of only 58 per cent. Zinn and Cosby [*32*] found an accuracy rate of 70 per cent for clinical diagnosis alone, without electrocardiographic aid. In this series it was found that an incorrect diagnosis, taking all the patients in groups II and III, was made more frequently than a correct one, as there were 148 incorrect diagnoses proved by autopsy and only 118 were correct.

This might seem to be a reflection upon the diagnostic skill of the physicians responsible, but almost half the patients died suddenly. Insufficient time was available for complete investigations and in many cases the patient died so unexpectedly that the diagnosis of myocardial infarction was made largely because of the precipitancy of the death. However, although the numbers are small, the impression is gained that the purely clinical diagnosis of myocardial infarction is grossly inaccurate. In the group of patients who had "non-sudden deaths" sent to postmortem with a diagnosis of myocardial infarction, but without electrocardiographic proof, there were only half as many (thirteen) correct as incorrect (twenty-four) diagnoses.

Parkinson and Bedford [*26*] defined three types of clinical presentation, one with sudden death, another with characteristically severe pain, and a third with breathlessness, or other signs, but

without pain. It is in the first and last types of case that the errors in diagnosis, both of omission and commission, are made. The clinical features of the classic case of myocardial infarction have been described with brilliant clarity by many authors [*10,13,14,19,26*], and such cases seldom give rise to diagnostic errors, except in those instances, of which there were fourteen in this series, when typical, severe symptoms are due to gross coronary artery sclerosis alone without actual infarction. Any condition that presents with severe pain in the chest or breathlessness—dissecting aortic aneurysm, acute left ventricular failure, pericarditis, cor pulmonale, pneumonias—may be a source of error. Acute upper abdominal emergencies have long been cited [*18*] as differential diagnoses; but only two errors of this type were found in this investigation, in a hospital dealing with hundreds of abdominal emergencies and myocardial infarctions yearly. Clearly a careful history and physical examination will distinguish between abdominal emergencies and myocardial infarction in the vast majority of cases.

The differential diagnosis between massive pulmonary embolism and myocardial infarction may be very difficult [*11*] but it is often only of academic interest as the patient dies within a very short time. The difficulties may be judged from the fact that almost as many patients were thought to have had pulmonary emboli and found to have had myocardial infarcts (nine), as were thought to have had infarcts and found to have had emboli (fourteen). One patient in whom a deep vein thrombosis had already developed suddenly became acutely dyspnoeic and died within an hour, but from massive myocardial infarction and not from pulmonary embolism.

It was found that of the patients dying suddenly from myocardial infarction a high proportion (74 per cent) had a previous history of coronary artery disease; and all those with electrocardiographic evidence of coronary artery disease before death who died suddenly died from myocardial infarction. Therefore a previous history of ischaemic heart disease in a patient who collapses or dies suddenly weighs heavily in favour of a diagnosis of myocardial infarction.

The majority of reports of sudden deaths refer to coroner's cases, the patients dying in the street or at their work. Hamman [*12*] found that non-valvular heart disease accounted for 48 per cent of cases of sudden death, and Bedford [*5*], reviewing 198 cases seen between 1910 and 1930, found a cardiac cause to be present in 122 cases; eighty-seven of these were non-valvular lesions, of which eighty were cases of coronary artery disease. The circumstances of death in this series are not entirely comparable for many of the patients had been under observation for some time before they died. In the two years under study seventy-four of the 132 patients dying suddenly in the wards died from myocardial infarction.

The difficulty of diagnosing myocardial infarction during the postoperative period has been recognised for a long time [*21,23*]. The chief difference between the usual and the postoperative syndrome is the frequent absence of pain in the latter [*16*]. The incidence of this complication was found to be 0.075 per cent. (Fifteen cases in 20,000 operations) by Wroblewski and LaDue [*30*]. It usually occurs within the first three to five days after operation, and carries a mortality rate of 40 to 60 per cent [*21,30*] and hypotension during and after the operation appears to be of particular aetiologic importance. The more frequent use of electrocardiography in the investigation of unusual postoperative syndromes was urged twenty-five years ago [*23*] and this is still, perhaps, a lesson incompletely learned.

The conditions diagnosed clinically in the patients in group III are those that mask myocardial infarction. Cases presenting as congestive and left-sided heart failure predominate. Robertson [*27*] has already drawn attention to the aetiologic relationship of "silent" myocardial infarctions to unexplained pleural effusions in people over forty years of age; and the findings here emphasized that congestive failure is not a diagnosis by itself, especially in the elderly person, for the average age of the fourteen patients in group III sent to autopsy with a provisional diagnosis of congestive or left-sided heart failure was seventy-four years. The onset of unexplained heart failure in this age group should raise the suspicion of underlying myocardial infarction.

The simultaneous occurrence of cerebrovascular accidents and myocardial infarcts has been previously noted by Bean et al. [*4*], who drew attention to those cases in which the hemiplegia resulted neither from cerebral haemorrhage nor thrombosis but from ischaemic changes secondary to hypotension. However, in this series all the patients had either cerebral haemorrhages or major thromboses, but in none of them was there evidence that the cerebral

damage was due to embolism from mural thrombi adhering to a recent myocardial infarct. In a recent survey in this department [*25*] of the electrocardiographic findings in fifty unselected cases of cerebral haemorrhage and thrombosis, only six patients were found to have a normal electrocardiogram and thirty-two patients were found to have had myocardial infarcts, either old or recent. That myocardial infarcts and cerebrovascular accidents not uncommonly occur coincidentally draws further attention to the unity of degenerative vascular disease, presenting now in one way, now in another, but seldom affecting a single section of the vascular tree alone.

Much has been written about the accuracy of electrocardiographic diagnosis [*1–3,7–9,17,32*]. So far as the clinician is concerned, the question to be answered by taking an electrocardiogram is "Has the patient had a myocardial infarct?" Therefore, the accuracy of the electrocardiogram in determining the precise site of infarction is of minor importance and has not been considered here. Using various criteria, several grades of diagnostic accuracy from 52 to 94 per cent, have been reported [*2,7*]. Most authors agree that old infarction may be very difficult or impossible to diagnose electrocardiographically, but that the diagnosis of recent infarction is very accurate, and certainly no patient with a recent infarct will have a consistently normal twelve lead electrocardiogram.

Feil et al. [*8*] found that a correct electrocardiographic diagnosis had been made in twenty-eight of thirty-four cases using three standard leads and two chest leads. The accuracy rate was 100 per cent with single recent infarcts, and 70 per cent when combined old and recent infarcts were present. Gray [*9*], using twelve leads, found that 77 per cent of acute infarcts were diagnosed correctly, but only 30 per cent of old infarcts. After a detailed study of the electrocardiographic findings in 149 consecutive autopsy cases Katz et al. [*17*] concluded that the criteria used by them in diagnosis were accurate, and in no case was a patient with any abnormality in the electrocardiogram found at autopsy to have a normal heart.

In our experience the electrocardiographic diagnosis of recent myocardial infarction is very accurate, only six incorrect diagnoses being made in ninety-seven cases. Since left bundle branch block—a pattern known to mask nearly all the changes of infarction—was found in half the cases, and subendocardial infarction only was found at necropsy in two of the others, the degree of accuracy was, if anything, greater than represented.

The need for serial tracings and multiple chest leads, if the greatest possible accuracy is to be obtained, has previously been emphasized [*15,17*]. Failey [*7*] and Zinn and Cosby [*32*] found a significant increase in diagnostic accuracy by the use of augmented unipolar limb leads and six praecordial leads. The use of these additional leads increases the possibility of a correct diagnosis by twenty to forty per cent and means that errors are due to faulty interpretation rather than lack of information.

In view of these findings, and since the purely clinical diagnosis of myocardial infarction tends to be inaccurate, it would seem inadvisable to rule out this diagnosis until adequate electrocardiographic investigations have been undertaken with serial twelve lead tracings; and it would further seem that in even the most typical cases the diagnosis should be confirmed electrocardiographically as soon as possible, for the purpose of both directing treatment and documenting for future reference the correctness of the clinical impression.

SUMMARY

1. Two hundred and sixty-six postmortem records of a consecutive series of patients found to have died from myocardial infarction, or suspected of dying from this cause in the Royal Infirmary, Edinburgh, during the years 1954 and 1955 have been reviewed.

2. In this hospital the accuracy rate in the diagnosis of myocardial infarction is surprisingly low, only 44 per cent when the examples revealed at autopsy and unsuspected clinically are taken into account. The major diagnostic errors occurred in patients who died suddenly or presented in an atypical way.

3. A greater awareness of the possibility of underlying myocardial infarction in elderly patients with unexplained heart failure or pleural effusions, in patients with cerebrovascular accidents, and in postoperative patients whose condition inexplicably deteriorates might lead to a decrease in diagnostic errors.

4. About 50 per cent of sudden deaths are due to myocardial infarction; anyone who dies suddenly, having given previous evidence, either clinical or electrocardiographic, of coronary artery disease is almost certain to have died in this way.

5. The electrocardiographic diagnosis of recent myocardial infarction is very accurate, and a clinical diagnosis alone without electrocardiographic corroboration, when this is available, is no longer justifiable.

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Seminar on Atherosclerosis

Hormonal Influences on the Serum Lipids*

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HORMONAL influences on carbohydrate and protein metabolism have been extensively studied. The role of the pancreas, the thyroid and the pituitary-adrenal "axis" in carbohydrate metabolism, and that of the gonads in protein metabolism, is well established by clinical observations in man and by extensive studies in the experimental animal. In contrast, information concerning hormonal influences on lipid metabolism is limited, although evidence is accumulating that such mechanisms exist and probably are important [*1*]. It is established, for example, that hypothyroidism and hyperthyroidism alter lipid metabolism, especially the cholesterol content of the serum [*2*]. Crude extracts of the anterior pituitary produce an increase in the lipid content of the liver and provoke ketonuria [*3*]. Following pancreatectomy, there is increased mobilization of fat, with an elevation of serum lipids and production of ketone bodies; these phenomena can be reversed by insulin administration [*4*]. It has long been suspected that the adrenal cortex plays an important role in lipid metabolism. Clinical observation suggests that hyperfunction of the adrenal cortex (Cushing's syndrome) produces hypercholesterolemia and an abnormal distribution of body fat, whereas adrenal insufficiency (Addison's disease) is associated with a low serum cholesterol and a loss of body fat [*5*].

The concept that atherosclerosis is a metabolic disorder [*6*] involving chiefly lipids and lipoproteins has stimulated extensive investigation of the endocrine influences on circulating lipids and on lipid metabolism. Even in countries with high dietary fat consumption there is still an individual susceptibility to atherosclerosis [*7*] which cannot be explained by environmental factors only [*8*]. There is evidence that hereditary influences determine the individual susceptibility to atherogenesis, presumably through genetically controlled enzymatic reactions [*6*]. The endocrine system may play an important regulatory or mediating role in these mechanisms.

The Thyroid. The role of the thyroid in the control of serum lipids is better established than that of the other endocrine glands [*2,9*]. Total thyroidectomy in man and in experimental animals results in a decided elevation of serum lipids [*10,11*]. According to our own studies [*12*], the elevation of the individual lipid fractions varies with the species. (Table 1.) In rabbits there is a moderate increase in serum cholesterol affecting total and esterified cholesterol approximately equally (+54 per cent and +47 per cent, respectively), in serum phospholipids (+30 per cent), and in serum triglycerides (+178 per cent); the more pronounced rise in triglycerides is mainly responsible for the increase of serum total lipids (+103 per cent). The failure of thyroidectomy to produce marked elevation of serum cholesterol in rabbits, and to enhance atherogenesis, was previously reported by Turner and Kayat [*13*].

In contrast, dogs after thyroidectomy exhibit a greater elevation of total and esterified serum cholesterol (+169 and +112 per cent) and of serum phospholipid (+53 per cent) than of serum triglycerides (+10 per cent); the increase in serum total lipids (+60 per cent) in the dog is mainly caused by the higher levels of serum cholesterol and phospholipid.

It is of interest that in man with hypothyroidism the diagnostic importance of hypercholesteremia is limited in adults but is greater in hypothyroidism in children [*14,15*]. It may best

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TABLE 1

EFFECT OF THYROIDECTOMY ON PLASMA LIPIDS IN RABBITS AND DOGS

Animals (no.)	Control				Time after Thyroidectomy (mo.)	Peak Values after Thyroidectomy				Increase in % of Control Value			
	Cholesterol Total/ Esterified	Phospholipid	Triglycerides	Total Lipids		Cholesterol Total/ Esterified	Phospholipid	Triglycerides	Total Lipids	Cholesterol Total/ Esterified	Phospholipid	Triglycerides	Total Lipids
Rabbits 20.....	41/32	87	112	240	2	63/47	113	311	487	54/47	30	178	103
Dogs 9.....	144/112	290	274	708	2.5	388/238	443	302	1133	169/112	53	10	60

NOTE: All values are expressed in mg./100 ml.

be used as a guide in substitution therapy of hypothyroidism, again especially in children [*16*]. In contrast to hypothyroidism, patients with hyperthyroidism exhibit a tendency to lower serum lipid levels, especially to hypocholesteremia [*17*]. However, this trend is not constant enough to be of practical value in the diagnosis of hyperthyroidism. The hypocholesteremia of hyperthyroidism also is of lesser value as a guide in the therapy of this condition than the hypercholesteremia in the management of hypothyroidism [*16*].

Desiccated thyroid and thyroid extracts reduce the serum cholesterol and phospholipid [*17*]. Because of possible implications in atherogenesis and perhaps in the therapy of atherosclerosis, especially of coronary atherosclerosis, there has been increased interest recently in the effects of thyroid-stimulating hormone (T.S.H.), desiccated thyroid, thyroid extract, thyroxin and related compounds on serum lipids and lipoproteins. T.S.H. has no direct effect on serum lipids and lipoproteins in patients with primary myxedema; its action in euthyroid subjects is probably mediated through stimulation of functioning thyroid tissue [*18*]. Prolonged administration of comparatively large doses of desiccated thyroid (260 to 325 mg. daily) produces a sustained fall in circulating serum cholesterol and lipoproteins [*19*]. The fall appears to depend upon the initial level, in that the higher the initial level of serum cholesterol or of the various lipoprotein fractions (Sf 0–12, Sf 12–20, Sf 20–100 and Sf 100–400) the greater is the decline with thyroid treatment. A possible interpretation of these observations is that patients with high serum cholesterol or corresponding serum lipoprotein levels may present a relative deficiency of the particular thyroid function which affects serum cholesterol and serum lipoproteins [*19*]. Escape phenomena observed with the use of somewhat smaller doses of desiccated thyroid (195 mg. daily) were not observed with the higher doses. After cessation of thyroid treatment a rebound in levels above the initial values was observed, probably caused by diminished endogenous production of thyroid hormone.

Patients with myxedema treated with L-thyroxine (sodium salt) showed depression of serum cholesterol, of the cholesterol-phospholipid ratio, and of the beta-lipoprotein cholesterol, with elevation of the alpha-lipoprotein cholesterol [*7*]. Reduction of the beta-lipoprotein fraction after thyroxine administration was previously observed by Malmros and Swahn [*20*]. Similar changes were seen in euthyroid patients with coronary artery disease and high plasma cholesterol levels under treatment with L-thyroxin or L-triiodothyronine. There was a fall in plasma cholesterol (−27 per cent), in the cholesterol-phospholipid ratio (−17 per cent), and in beta-lipoprotein cholesterol; but in contrast to patients with myxedema, there was no corresponding elevation in alpha-lipoprotein cholesterol [*18*].

The failure of L-thyroxine and L-triiodothyronine to raise alpha-lipoprotein cholesterol is of interest. In patients with Graves' disease under treatment with antithyroid drugs or radioactive iodine and in patients with myxedema under treatment (presumably with desiccated thyroid or triiodothyronine) Barr [*21*] observed the expected changes in serum cholesterol and/or basal metabolic rates with only "trivial" changes in alpha-lipoprotein cholesterol. Intravenous administration of triiodothyronine in one patient with myxedema (basal metabolic rate, 38 per cent) resulted in a decrease of serum cholesterol from 456 to 338 mg. per cent but without affecting the distribution of cholesterol between alpha- and beta-lipoprotein. On the other hand, Marmorston et al. [*22*] found diminished thyroxine production in postmenopausal women and they

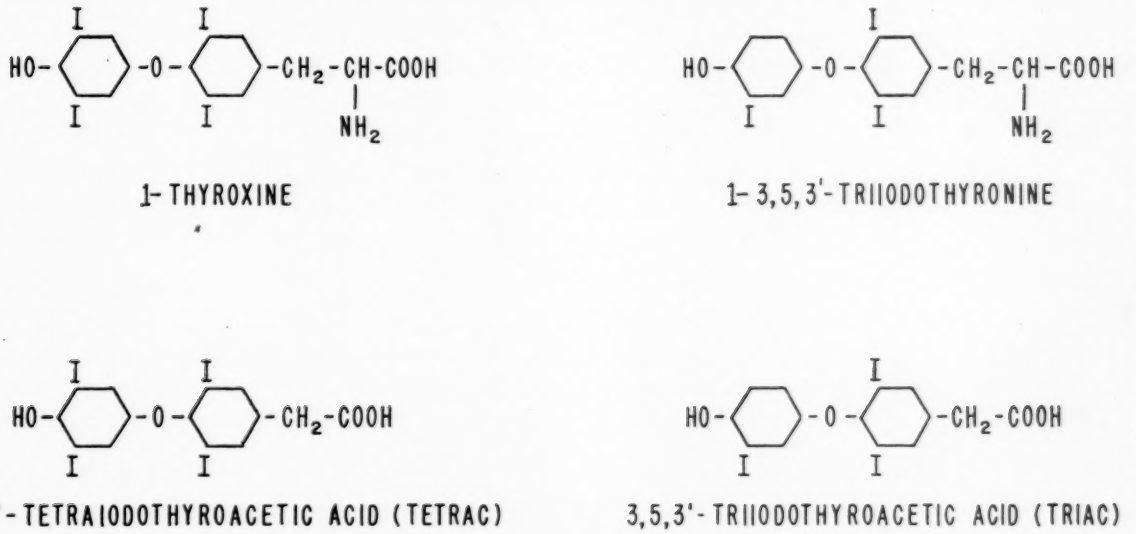


FIG. 1. Chemical structure of L-thyroxin, L-triiodothyronine, tetrac and triac.

believe that this factor may play an important role in the occurrence of myocardial infarction.

The acetic acid analogues of thyroxine and triiodothyronine have received special attention recently because of their alleged capacity to lower circulating lipids, especially serum cholesterol, without causing significant changes in the basal metabolic rate. These compounds differ from thyronine and triiodothyronine in that the alanine sidechain is replaced by acetic acid. (Fig. 1.) The acetic acid analogue of thyroxine was synthesized by Harrington and Pitt-Rivers in 1952 (tetraiodothyroacetic acid, or tetrac) [*23*]; the corresponding analogue of triiodothyronine was synthesized a year later by Pitt-Rivers (triiodothyroacetic acid, or triac) [*24*]. Unlike thyroxine and triiodothyronine, triac has an immediate effect on the oxygen consumption of kidney slices *in vitro* and causes an almost immediate increase in the oxygen consumption of thyroidectomized rats [*25*]. Triac has been identified in kidney slices incubated *in vitro* with triiodothyronine labelled with I^{131} [*26*]. It is believed that the oxidative deamination and decarboxylation of triiodothyronine to triac are physiologic steps in the mechanism of thyroid hormone action in the tissues and that triac normally is formed from triiodothyronine [*27a*].

Triac given to two patients with myxedema resulted in amelioration of the clinical signs and in marked fall of serum cholesterol without any change in the basal metabolic rate, which remained low [*28,29a*]. These initial observations suggested that triac, when compared with thyroxine, may exert a greater effect on serum cholesterol than calorigenically, and that because of lack of calorigenic effects may prove to be useful in the treatment of euthyroid persons with hypercholesteremia (idiopathic hypercholesteremia and idiopathic hyperlipemia) [*27b*]. Unfortunately, it is doubtful at present whether or not triac and tetrac are suitable agents for long term treatment.

The effect of these hormones varies with the patient. Although triac appeared to have a relatively greater effect on the serum cholesterol levels in myxedema than thyroxine, triiodothyronine was about seventy-five times more effective than triac both in depressing plasma cholesterol and in elevating the basal metabolic rate [*28*]. In euthyroid patients, the plasma cholesterol lowering effect of 2 to 4 mg. triac daily was comparable with that of 0.08 mg. of triiodothyronine. In three of eighteen patients there was no obvious rise in the basal metabolic rate although the plasma cholesterol level was reduced [*28*]. Tetrac was compared in its effects with L-thyroxine in a careful study in one patient with myxedema [*29b*]. In a daily dosage of 8 mg. tetrac produced a clinical remission and reverted the plasma cholesterol level and the basal metabolic rate to normal. Its potency was found to be about one-thirtieth of that of L-thyroxine [*29b*].

These observations might be compatible with the concept that the control of metabolism and regulatory influence on circulating lipids and lipoproteins may represent two separate func-

tions of the thyroid. Strisower et al. [*19*] advise caution in evaluating these new substances. They found that desiccated thyroid may produce well marked effects on serum lipids in many patients without significantly altering the body weight and concluded that undesired adverse

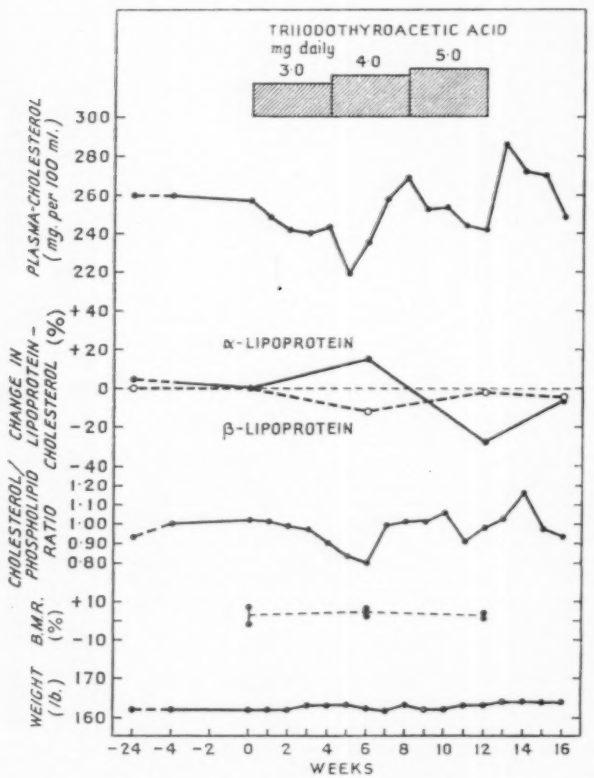


FIG. 2. Effects of increasing doses of triac (3.0 to 5.0 mg. daily) on the plasma levels of lipids and lipoproteins, the basal metabolic rate and on the weight of six euthyroid men with coronary disease OLIVER, M. F. and BOYD, G.S. *Lancet*, 1: 124, 1957 [*30*].

effects, e.g., weight loss and increased basal metabolic rate, need not arise in treatment with desiccated thyroid. Oliver and Boyd [*30*] studied the influence of triac on plasma cholesterol, phospholipid and on the distribution of cholesterol between alpha- and beta-lipoprotein (zone electrophoresis with subsequent elution of cholesterol). Their subjects were middle-aged men (thirty-three to forty-nine years of age) who had suffered myocardial infarction at least nine months prior to the trial with triac. Lowering of plasma cholesterol, of the cholesterol-phospholipid ratio and of the beta-lipoprotein cholesterol was observed without elevation of the basal metabolic rate. Unfortunately, in two of the twelve men angina of effort and decrease in exercise tolerance developed during therapy. The depression of plasma cholesterol could not be maintained over long periods of time even when the daily dosage of triac was raised from 3 mg. to 4 mg. and then to 5 mg. (Fig. 2.) The larger dosage of triac may be undesirable because it may cause angina more readily. It was concluded that triac "may not prove suitable for the long term control of hypercholesteremia in patients with clinical coronary disease" [*30*].

Thus, additional extensive studies are necessary to delineate the possible role of the thyroid and the various thyroid hormones and analogues in the control of hypercholesteremia in euthyroid persons, especially in the presence of clinical coronary disease.

The Gonads. Evidence is accumulating that the gonads exert an important influence on the level of circulating lipids and lipoproteins. The comparatively rare occurrence of coronary artery disease in women during the reproductive phase is well known [*31,32*]. Bilaterally oophorectomized women show a higher incidence of coronary artery disease than normal women of corresponding ages [*33*]. The higher incidence of coronary atherosclerosis after the menopause is usually explained by decreased gonadal function [*31,32*], perhaps also by diminished thyroid function [*22*].

Age and sex affect serum lipid levels in man [*34–36*]. Dietary factors, particularly dietary fat, appear to be related to serum lipid concentrations [*37–41*]. The role of other factors, such as ethnic origin, occupation, stress, physical activity, smoking and alcohol, is questionable [*38,42*].

Observations on serum cholesterol levels in various population groups have been reported by Page et al. [*43*], Barker [*44*] and Kornerup [*45*]. More recently Keys et al. [*34*] studied 2,056 men aged seventeen to seventy-eight years in a middle-income group in Minnesota. McMahon et al. [*35*] performed 822 serum cholesterol determinations in 554 normal persons aged ten to ninety years. Epstein and Boas [*46*] included serum cholesterol studies in their observations on the prevalence of manifest atherosclerosis in a working population in New York that consisted mainly of Jews and Italians. Keys and co-workers [*47–49*] extended their cholesterol studies to population groups in England, Southern Italy (Naples) and Spain (Madrid). Oliver and Boyd [*31,50*] performed plasma cholesterol determinations in control groups of men and women aged thirty to over seventy years in Scotland. Walker and Arvidsson [*42*] studied the

changes with age in serum cholesterol levels in the South African Bantu. Adlersberg et al. [*51*] examined approximately 1,200 healthy males and females between the ages of two and seventy-seven years of low middle income in New York. The almost completely white population was

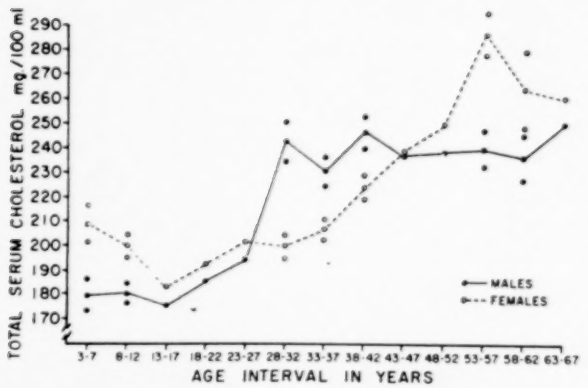


FIG. 3A. Total serum cholesterol levels by age in males and females. ADLERSBERG, D., SCHAEFER, L. F. and STEINBERG, A. *J. A. M. A.*, 162: 619, 1956 [*51*].

otherwise moderately heterogeneous, with a distinct predominance of families of Italian and Irish origin. The total serum cholesterol level of the males remained constant from age two through nineteen. From age twenty through thirty-three there was a significant increase of total cholesterol level, averaging 3.6 mg. per cent per year. Thereafter, until age sixty, there was no further change. The total serum cholesterol level of the females did not change significantly from age two through thirty-two, although there appeared to be a slight decrease from age two through twenty. From age thirty-three through fifty-eight a significant rate of increase of 3.2 mg. per cent per year occurred. (Table II and Fig. 3A.)

The changes in serum phospholipid levels with age were similar to the changes in serum cholesterol levels in the two sexes. (Fig. 3B.) There were no significant differences between the sexes or between any age groups in respect to the ratio of free to total cholesterol. The cholesterol-phospholipid ratio appeared to be a function of the change in the serum cholesterol level and was independent of age. For each increase in the serum cholesterol level of 1 mg. per cent, there was an increase of 0.71 mg. of phospholipid in the serum in the females and of 0.67 mg. in the males. In other words, as the serum cholesterol level increased, the ratio of cholesterol to phospholipid became greater. The differences between males and females in respect to changes in lipid levels with age are worthy of note. The period of marked increase of serum lipid levels which occurs physiologically in both sexes starts thirteen years later in women than in men and lasts twelve years longer.

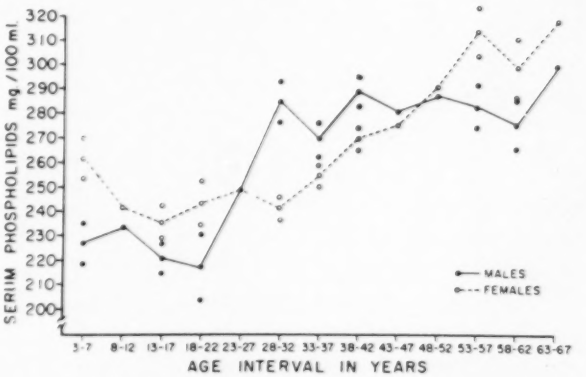


FIG. 3B. Serum phospholipid levels by age in males and females. ADLERSBERG, D., SCHAEFER, L. F. and STEINBERG, A. *J. A. M. A.*, 162: 619, 1956 [*51*].

TABLE II
CHANGES IN SERUM CHOLESTEROL LEVEL WITH AGE IN MALES AND FEMALES [*51*]

Age Interval (yr.)	No.	b*	P†
	Males		
2–19	154	−0.278	>0.20
20–33	74	3.622	0.01>P>0.001
34–50	213	−0.445	>0.20
51–60	96	−0.821	>0.20
	Females		
2–13	100	−1.478	>0.20
14–20	58	−2.065	>0.20
21–32	104	−1.077	>0.20
33–58	263	3.181	<0.001

* The average annual change of total serum cholesterol in mg./100 cc. is represented by the coefficient b in the regression equation $Y = a + bX$, where X = age in yr. and Y = serum cholesterol level.

† Probability that the true value of the average annual change may be zero.

It may be postulated from the data derived from this study that the large annual increments in average serum lipid levels in men from age twenty through thirty-three play a part in producing the higher frequency of coronary artery disease in males in the younger decades, and that increasing incidence of the disease in females in the older age groups may be related to the

analogous changes occurring in women starting thirteen years later and lasting twelve years longer than in men. The proof of this hypothesis will require a longitudinal study extending over a number of years. Careful observations on the frequency of coronary artery disease in males and females in relation to serum lipid and lipoprotein levels would be the goal of such an investigation.

Sex differences in the distribution of serum lipoproteins have been reported by various laboratories using the Cohn protein microfractionation technic [*52*], the ultracentrifuge technic [*53*] and zone electrophoresis with subsequent elution [*54*]. Normal young women have a relatively greater cholesterol concentration in the serum alpha-lipoprotein fraction, and correspondingly smaller amounts of cholesterol in the beta-lipoprotein fraction, than normal men of corresponding ages. This difference is not apparent after the menopause.

Systematic studies on the effects of estrogens and androgens added important evidence to the effects of the gonads on circulating lipids and lipoproteins. Most of the experimental work with estrogens was performed in the chick. Large doses of estrogens (diethylstilbestrol) added to a normal diet produced lipemia in the chick and increased atherogenesis [*55,56*]. However, estrogens inhibited atherosclerosis in the cholesterol-fed chick and caused regression of pre-existing coronary lesions [*57–60*]. Apparently then, estrogens and cholesterol, administered alone, produce atherogenic effects in the chick but when given together estrogens seem to counteract the effect of cholesterol feeding.

Considerable information is available as to the effects of gonadal hormones in man. Eilert reported in 1949 on the effect of estrogens in pre- and postmenopausal women. A decided reduction in plasma cholesterol and the cholesterol-phospholipid ratio was observed [*61*]. Extensive studies on the effects of estrogens and androgens in patients who survived myocardial infarction were later reported by several investigators [*7,21b,62*]. Synthetic or naturally occurring estrogens corrected the abnormal lipid and lipoprotein pattern of survivors of myocardial infarction. They lowered plasma cholesterol and raised the cholesterol concentration of the alpha-lipoproteins and correspondingly diminished the cholesterol concentration of the beta-lipoproteins. In many instances complete restoration of normal patterns was achieved. In primary hypercholesteremic xanthomatosis qualitatively similar changes in plasma cholesterol and lipoproteins were observed without restoration of normal patterns.

Administration of progesterone to men with coronary artery disease and hypercholesteremia failed to produce significant changes in plasma cholesterol, cholesterol–phospholipid ratio and beta-lipoprotein cholesterol, despite an increase in alpha-lipoprotein cholesterol [*7*]. Because of the small number of subjects observed (six) and the short duration of progesterone administration (five days) these studies require repetition on a larger scale.

Methyl testosterone produced effects opposite to those of estrogens. It exaggerated the lipid and lipoprotein alterations in the plasma of survivors of myocardial infarction. The estrogenic effects were modified or obliterated by the simultaneous use of estrogens and androgens [*7,21b*].

The use of large doses of estrogens such as 1.0 mg. estinyl or 10 mg. premarin® daily produced severe systemic changes: Gynecomastia, complete impotence, restlessness, depression and not infrequently nausea and gastric distress. Robinson et al. [*62*] treated a group of men with myocardial infarction for periods of six to forty-eight months with estrogens (average 10 mg. of mixed conjugated estrogens (premarin)). A decrease in serum total cholesterol, with increase in phospholipid and in alpha-lipoprotein cholesterol was observed. Sexual potency gradually decreased and eventually became absent. Gynecomastia proved to be so distressing that in the younger age group surgical removal of the glandular tissue of the breast was performed prior to institution of estrogen therapy.

Testicular biopsies showed fibrosis of tubular cells and severe atrophy or complete absence of Leydig cells. The severe testicular atrophy represented probably irreversible damage. (Fig. 4.) I^{131} uptake was not changed by the administration of these large doses of premarin for one year. The changes in serum lipids were not considered to be caused by increased thyroid function. It is clear, then, that massive estrogen therapy must be regarded as still an experimental approach to this problem [*62*].

It is of interest that much smaller dosages of estrogens than those mentioned can rectify abnormal serum lipid and lipoprotein patterns and restore them to normal. This form of hormonal therapy is associated with less severe

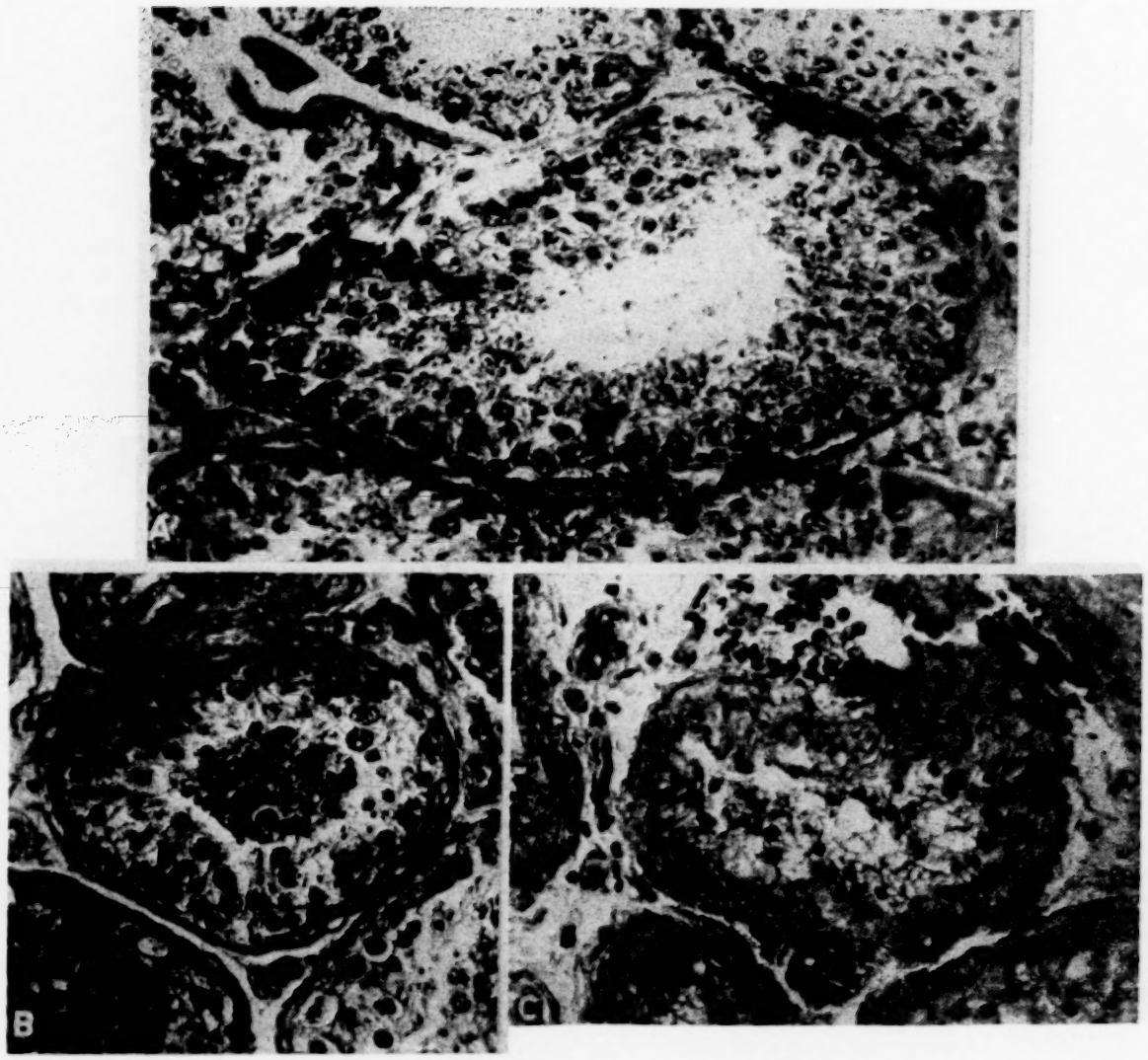


FIG. 4. A, Testicular biopsy before estrogen therapy. Normal spermatogenesis. B, Testicular biopsy one month after institution of estrogen therapy (0.3 gm. total). Hypospermatogenesis with arrest of spermatocytogenesis at primary spermatocyte level. Moderate thickening of tubular tunica propria. C, Testicular biopsy twelve months after institution of estrogen therapy (3.65 gm. total). Aspermatogenesis with tubules lined by atrophic lipid-filled Sertoli cells. Marked thickening of tubular tunica propria. Leydig cells not identifiable. ROBINSON, R. W et al. *Circulation*, 14: 365, 1956 [*62*].

adverse effects. Oliver and Boyd [*63*] treated ten men with daily doses of 0.2 to 0.6 mg. of ethinyl estradiol over a period of more than eleven weeks. An average depression of total plasma cholesterol of 25 per cent was achieved ($P < 0.01$); the cholesterol: phospholipid ratio showed an average fall of 29 per cent ($P < 0.01$). Even with these smaller doses, gynecomastia, nausea, dizziness, fatigue and depression were common complaints and loss of libido occurred in some subjects. In a later report similar chemical changes were maintained over periods of one and two years with daily doses of 0.2 mg. ethinyl estradiol [*7*].

In our laboratory the effects of long term treatment with low doses of ethinyl estradiol (estinyl) on the serum lipids and lipoproteins were studied in patients with idiopathic hyperlipemia and idiopathic hypercholesteremia [*64*]. Only patients who had been receiving therapy for a minimum of two months were included in this report. The group included four men and two women with idiopathic hyperlipemia (average age forty-eight years) and two men and three women with idiopathic hypercholesteremia (average age forty-seven years). Four patients had skin xanthoma and two had xanthoma tendinosa, five had coronary artery disease and

TABLE III

EFFECT OF PROLONGED ESTINYL ADMINISTRATION (TWO TO FOURTEEN MONTHS, AVERAGE EIGHT MONTHS) IN DAILY DOSES OF 0.1 TO 0.2 MG. ON SERUM LIPIDS AND LIPOPROTEINS (BY PAPER ELECTROPHORESIS)

Condition	No.	Average Age	Before Estinyl			After Estinyl		
			Cholesterol Total/Esterified	Phospholipid	Total Lipids	Cholesterol Total/Esterified	Phospholipid	Total Lipids
A. Lipids								
Idiopathic hyperlipemia	6	48	584/393	635	2909	290/198	441	1421
Idiopathic hypercholesteremia	5	47	467/358	428	1321	304/217	378	1040
B. Lipoproteins								
			Alpha	*Beta*	*O*	*Alpha*	*Beta*	*O*
Idiopathic hyperlipemia	6	48	11.9	35.5	50.6	23.2	40.4	36.4
Idiopathic hypercholesteremia	5	47	14.3	68.9	16.9	31.8	59.2	9.0

NOTE: Serum lipids are expressed in mg./100 ml., serum lipoproteins in percentages of stainable lipid.

one had recurrent acute pancreatitis. The average duration of therapy was eight months (range two to fourteen months). Doses ranged from 0.1 to 0.2 mg. daily. A low fat diet was instituted prior to and during the study. The body weight remained stable.

In both groups lipid levels were lower under estrogen therapy. Maximum effects were noted after approximately six weeks. (Table III.) In the hyperlipemic group, levels of serum total and esterified cholesterol decreased by 50 per cent, and total lipids by 51 per cent. The serum phospholipids showed a fall averaging 30 per cent. The beta-lipoprotein fraction rose slightly, from 35.5 per cent to 40.4 per cent, and the O (origin)-fraction decreased from 50.6 per cent to 36.4 per cent. There was, however, a marked increase in alpha-lipoprotein, from 11.9 per cent to 23.2 per cent of the total stainable lipid.

In the hypercholesteremic group, levels of serum total and esterified cholesterol decreased, by 35 and 39 per cent, respectively, and average serum phospholipids by 12 per cent. Total lipids fell 21 per cent. Beta-lipoprotein decreased from 68.9 per cent to 59.2 per cent, the O-fraction decreased from 16.9 per cent to 9.0 per cent and alpha-lipoprotein increased from 14.3 per cent to 31.8 per cent of the total stainable lipid.

Levels of lipids and lipoproteins on placebo therapy were unchanged from control levels. Moderate gynecomastia and diminished libido were observed uniformly in men. In two postmenopausal women mild uterine bleeding occurred. In two patients the cardiac status improved, in three it was unchanged. In one patient with idiopathic hyperlipemia and extensive xanthoma tuberosa there was gradual disappearance of the lesions during fourteen months of estrogen therapy. (Fig. 5.) This is in agreement with the observation of Russ, Eder and Barr [*21b*] in their patient Sen who also had idiopathic hyperlipemia. However, similar effects were observed by us and others in patients with xanthomatosis and idiopathic hyperlipemia on low fat diets administered for prolonged periods of time without the use of estrogens [*65,66*]. (Fig. 6.)

It is thus evident that considerable reduction of serum lipids and beta-lipoproteins can be achieved on constant diets in patients with idiopathic hyperlipemia and idiopathic hypercholesteremia with relatively small doses of estrogens without disturbing side effects. Our present regimen in men and non-hysterectomized women consists of three weeks of estrogen therapy and one week without medication. It permits maintenance of lower serum cholesterol and beta-lipoprotein levels, with only mild adverse effects. Serial testicular biopsies will prove or disprove the ultimate value of this therapy in the management of patients with these two inborn errors of lipid metabolism and perhaps in

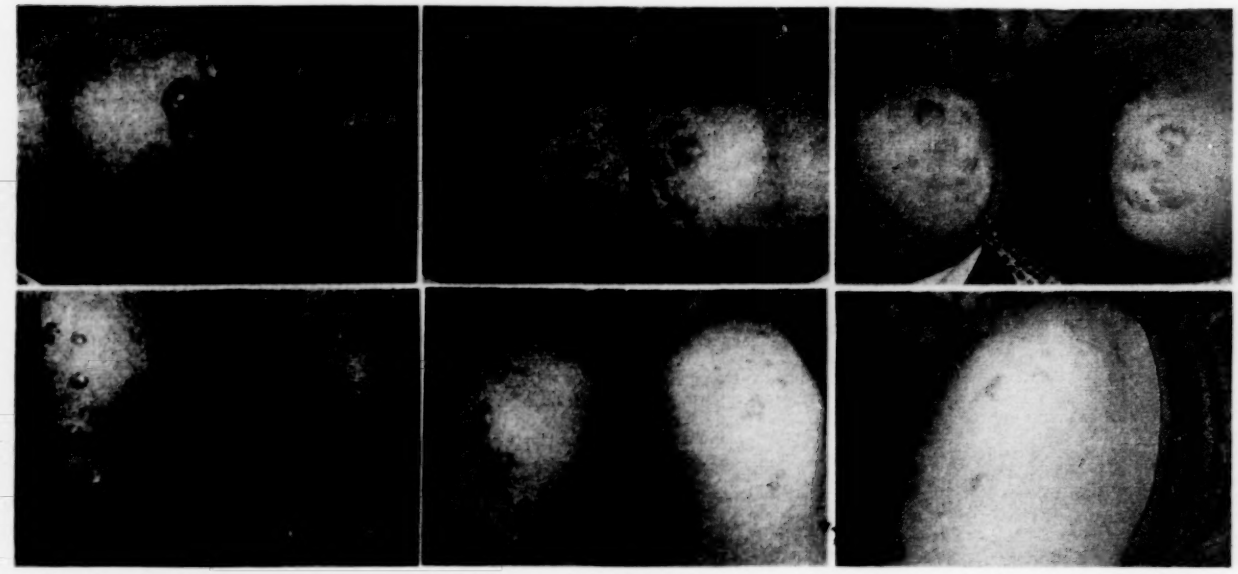


FIG. 5. C. N. Idiopathic hyperlipemia, xanthoma tuberosum. (1) Elbows, prior to estinyl therapy. (2) Elbows, seven and a half months after institution of estinyl therapy 0.1 to 0.2 mg. daily. (3) Elbows, after repeated courses of estinyl therapy, fourteen months after institution. (4) Knees, prior to estinyl therapy. (5) Knees after seven and a half months of estinyl therapy. (6) Knees after fourteen months of estinyl therapy. Low fat diet maintained prior to and during estinyl therapy. Note marked regression of xanthoma tuberosum of elbows and knees.

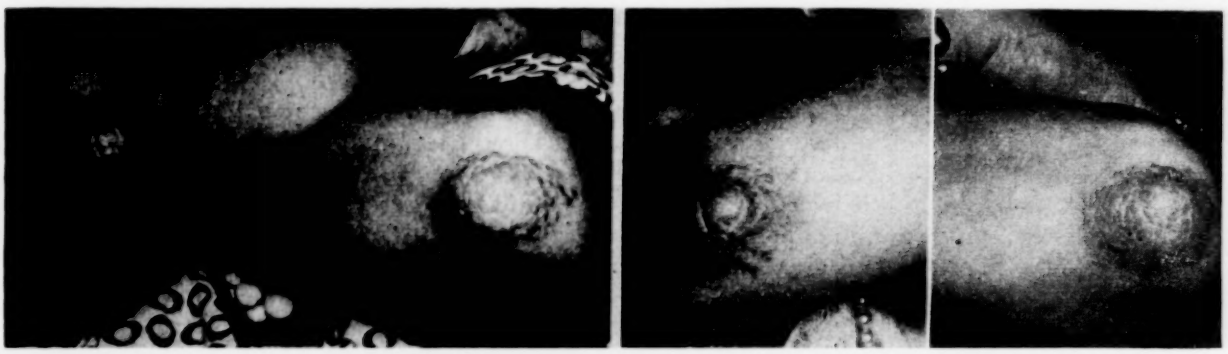


FIG. 6. S. V. Idiopathic hyperlipemia. Xanthoma tuberosum of both elbows. Left, prior to institution of dietary fat restriction. Right, after sixteen months. Note regression of xanthomata, especially of smaller nodes in the periphery of the lesions.

patients with coronary artery disease. Irreversible testicular atrophy would preclude the use of this form of gonadal therapy even in its modified milder form.

The Adrenals. The role of the adrenal cortex in lipid metabolism has been suggested by clinical observations in Cushing's syndrome and in Addison's disease [*5*]. The important position of the adrenal cortex in the biosynthesis of steroid hormones led Deuel to the assumption "that it would exert some control over the cholesterol content of the blood" [*67*].

Older studies failed to show changes in serum cholesterol after experimental adrenalectomy [*68–70*]. This is probably explained by the short survival time of these animals and perhaps by considerable loss of weight, water and electrolytes. Recent studies performed under adequate experimental conditions revealed a marked decrease in plasma phospholipid and cholesterol concentration in bilaterally adrenalectomized dogs maintained on DCA for periods ranging from eight to thirty-three days [*71–73*]. The main decrease of plasma phospholipid amounted to 50 per cent and that of total cholesterol to 48 per cent of the initial value. The substitution of cortisone for DCA resulted in a marked increase in the concentration of both plasma cholesterol and phospholipid, whereas discontinuation of cortisone and resumption of DCA therapy

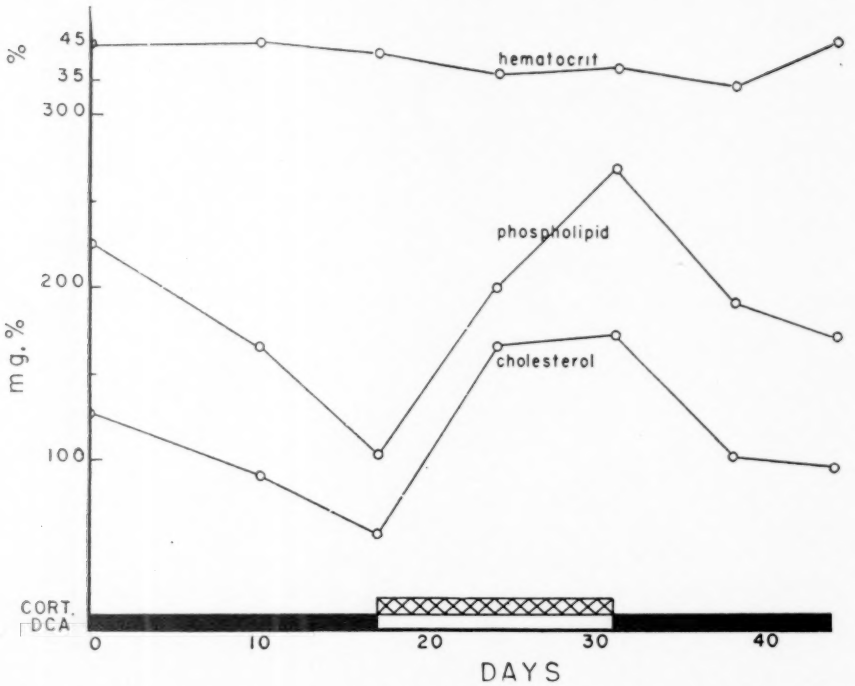


FIG. 7. The effects of alternate administration of desoxycorticosterone acetate and cortisone on plasma phospholipid and cholesterol concentrations of an adrenalectomized dog. Lipid values (mg. per cent) and hematocrit (per cent) are plotted against days after adrenalectomy. DI LUZIO, M. R., SHORE, M. L. and ZILVERSMIT, D. B. *Metabolism*, 3: 424, 1954 [*73*].

again caused marked lowering of both plasma lipid fractions. (Fig. 7.) On the basis of these observations [*73*], and of similar findings in patients treated with ACTH and cortisone in whom a striking parallelism between changes in serum cholesterol and phospholipid was observed [*74*], it was thought that these hormones control the metabolism of plasma cholesterol and phospholipid by the same mechanism. It was considered that this control might be effected through the regulation of protein metabolism in the liver and plasma; the parallel changes in the concentration of these two lipids might merely reflect changes in the concentration of those proteins of which cholesterol and phospholipid are integral parts [*73*].

The possibility that DCA given to bilaterally adrenalectomized dogs might *per se* produce a fall in plasma lipids, and its withdrawal an elevation of these fractions, was not supported by additional experiments. When the dosage of DCA was increased ten times a greater decline of plasma lipids was not seen. In addition, the withdrawal of DCA in these animals resulted, as expected, in adrenal insufficiency but was not associated with a rise in plasma lipid levels [*73*].

The hypothesis that cortisone influence plasma lipids was supported by the finding that bilaterally adrenalectomized dogs given both DCA and cortisone showed no decrease in plasma cholesterol and phospholipid concentrations. But when cortisone was withdrawn a marked fall of both fractions occurred. The observations in the bilaterally adrenalectomized animal are compatible with the hypothesis "that the adrenal cortex regulates plasma lipid concentrations by a direct action of cortisone on lipid or lipoprotein metabolism" [*73*].

Other animal experiments lend additional support to the concept that the adrenal cortex has a role in plasma lipid and lipoprotein metabolism. Ketonuria and fatty infiltration of the liver produced by anterior pituitary extracts, by pancreatectomy or by starvation could be prevented by adrenalectomy [*75a*]. After adrenal homotransplantation hypercholesteremia was observed in rabbits [*75b*].

Since the advent of the cortisones considerable information has accumulated regarding the effect of administration of these hormones on circulating lipids and lipoproteins. The observations in healthy experimental animals are more valid in this respect than those obtained in human patients with a variety of pathological conditions in whom these hormones were used for therapeutic purposes. Observations in normal

man are naturally limited by the quantity of the hormones that can be given and by the short duration of the administration. Serious adverse effects, such as altered cardiovascular dynamics, water and salt retention, gastrointestinal ulceration and perforation, and thromboembolic phenomena, represent a well recognized hazard and limit the use of these hormones for experimental studies in man. On the other hand, species differences in circulating lipids and lipoproteins [*76*] limit the applicability of animal experiments to man. One must always consider the possibility that administration of specific hormones results in functional changes of other endocrine glands and that the interrelationship of the endocrine glands again differs with the species. For instance, thyroidectomy affects in a different way the response of serum lipids to cortisone administration in man, in the dog and in the rabbit [*77*].

In rabbits, the administration of the cortisones produced an increase in plasma cholesterol, phospholipid, a nd especially triglycerides [*78–80*]. In many instances marked turbidity of the serum (lipemia) was observed. Similar changes in serum cholesterol and phospholipid were observed in the rat [*81,82*]. In contrast, in the dog cortisone and hydrocortisone produced only small increases in the plasma lipid fractions [*80*].

Comparative studies were made of the effects of prednisone, cortisone and hydrocortisone on plasma lipids and lipoproteins in the rabbit [*83*]. The increase in phospholipids and neutral fats occurred earlier and was more pronounced than that of cholesterol, resulting in moderate changes of the cholesterol : phospholipid ratio. The increase in serum cholesterol was due to a greater extent to a rise in the free rather than in the esterified fraction. The esterified cholesterol fraction decreased from 70 to 75 per cent of the total cholesterol to 35 to 60 per cent after thirty days. The decrease of esterified cholesterol was most pronounced following prednisone administration. Similarly, the elevations of all lipid fractions were decidedly higher after twenty and thirty days administration of prednisone than after cortisone and hydrocortisone administration. (Table IV.) There was a marked alteration in plasma lipoprotein patterns (Table V), characterized by a decrease of the alpha- and beta-lipoproteins and a concomitant increase of the O-fraction (lipoprotein adhering to the point of origin). Again, these changes were most pro-

TABLE IV

EFFECT OF PREDNISONE, CORTISONE AND HYDROCORTISONE ON THE PLASMA LIPID PARTITIONS OF THE RABBIT [*83*]

Corticosteroid	Animals (no.)	0				10 Days				20 Days				30 Days			
		Cholesterol Total/Esterified	Phospholipid	Total Lipids	Neutral Fat	Cholesterol Total/Esterified	Phospholipid	Total Lipids	Neutral Fat	Cholesterol Total/Esterified	Phospholipid	Total Lipids	Neutral Fat	Cholesterol Total/Esterified	Phospholipid	Total Lipids	Neutral Fat
Cortisone	12	55/41	112	306	139	59/37	154	655	442	69/29	212	1,090	809	75/45	181	822	566
Hydrocortisone	11	47/35	103	505	355	42/25	127	771	512	49/25	151	745	545	79/41	250	1,014	765
Prednisone	12	50/35	105	350	195	56/33	178	701	467	86/40	238	1,260	936	130/46	323	2,056	1,603

NOTE: All values are expressed in mg./100 ml.

nounced after prednisone administration. Elevation of the free plasma cholesterol level without a corresponding increase in the esterified fraction was seen in all groups of animals but was more pronounced during prednisone administration. These observations may indicate a metabolic

TABLE V

EFFECT OF PREDNISONE, CORTISONE AND HYDROCORTISONE ON PLASMA LIPOPROTEIN PATTERNS* IN THE RABBIT [*83*]

Corticosteroids	Animals (no.)	Days of Treatment (average)	Lipoproteins (% of total stainable lipids)		
			Alpha	Beta	O
None	16	0	30.7	50.4	18.9
Cortisone	2	14	10.2	30.8	59.0
Hydrocortisone	2	29	11.8	33.9	54.3
Prednisone	5	30	5.8	34.5	62.7

* By paper electrophoresis.

block in the esterification of cholesterol as part of the effect of these steroids on lipid metabolism. The marked increase in the level of plasma neutral fats may be related similarly to impaired esterification of fatty acids. In their studies on cortisone, Pierce and Bloom suggested a block of lipoproteins at the Sf 40–80 level [*84*]. The studies with labelled cholesterol and acetate in abnormal states of lipid metabolism in man also disclosed differences in the relation of plasma free and esterified cholesterol during the period of incorporation [*85*]. Thus the elevation of all plasma lipid fractions after prednisone, cortisone and hydrocortisone administration might be the result of increased synthesis, a metabolic block affecting esterification of fatty acids, or perhaps a combination of both mechanisms.

The combination of cortisone and hydrocortisone administration with cholesterol feeding resulted, in the rabbit, in enhanced elevations of all lipid fractions. (Table VI.) The plasma of these animals showed much greater turbidity than that of the other groups treated with cortisone or hydrocortisone alone or with cholesterol supplements alone. Despite extreme elevation of all lipid fractions, the cholesterol-fed hormone-injected animals exhibited less atherosclerosis than those treated with cholesterol alone. Hormonally-induced diminished permeability of the tissue was suggested to explain the experimental findings [*86,87*].

During cortisone therapy in man, especially when it was of prolonged duration, an elevation of serum cholesterol and phospholipid was not infrequently observed [*88*]. The clinical conditions for which this form of therapy was used included severe systemic diseases such as disseminated lupus erythematosus, scleroderma, rheumatoid arthritis, leukemia and acute rheumatic fever. An increase of serum cholesterol was observed in twenty-one of the twenty-six courses of therapy in twenty-two patients and amounted to 20 per cent [*88,89*]. The duration of treatment varied from six to 105 days and averaged twenty-five days. There was a concomitant elevation of the esterified cholesterol and phospholipid. Some of the serums became opalescent. Several patients showed changes in the distribution of body fat (buffalo-type obesity and moon face), resembling those seen in Cushing's syndrome.

Similar changes were observed in twenty-one courses in eighteen patients treated with ACTH for an average period of forty-eight days. Although it was difficult to determine the relative potency of cortisone and ACTH in producing hypercholesteremia, the impression derived was that cortisone produced a somewhat higher and more sustained level of serum cholesterol. With ACTH a moderate drop in total serum cholesterol was noted during the first few days of treatment, as originally observed by Conn et al. [*90*], but this was usually followed by a subsequent rise.

The production of hypercholesteremia in two patients who proved to be members of a hypercholesteremic family suggested the possibility that the use of these hormones may convert a patient who has such a familial predisposition from latent to overt hypercholesteremia [*88,91*].

In contrast to these observations, Oliver and Boyd [*7*] observed a fall in plasma cholesterol, in cholesterol-phospholipid ratio and in beta-lipoprotein cholesterol after cortisone injections had been given for ten days to patients with coronary artery disease. Similar results were observed after short courses of administration of corticotropin (five to eight days) and of desoxycortone acetate (five days). They believe that these results, obtained in hypercholesteremic subjects, do not contradict other observations [*88*] in which cortisone raised serum cholesterol in patients "severely ill with collagen diseases." Barr [*21a*] observed the effect of cortisone on serum lipids and lipoproteins in six normal men

TABLE VI

PLASMA LIPID FRACTIONS, MG. PER 100 ML., OF THE RABBIT UNDER VARIOUS EXPERIMENTAL REGIMENS, 1 GM. CHOLESTEROL PER ANIMAL PER DAY [*87*]

Group	Animals (no.)	After 4 Weeks			Additional Treatment	After 2 Weeks			After 4 Weeks			Degree of Atherosclerosis	
		Cholesterol Total/ Esterified	Phospholipid	Total Lipids		Cholesterol Total/ Esterified	Phospholipid	Total Lipids	Cholesterol Total/ Esterified	Phospholipid	Total Lipids	Aorta	Pulmonary Artery
A	9	1006/723	464	2362	None	1223/923	493	3030	1380/1060	486	3270	1.2	0.9
B	5	1098/822	398	2380	Cortisone 3.75 mg. daily	2232/1685	785	5040	3501/2392	1031	6969	0.5	0.4
C	13	1013/744	469	2171	Hyaluronidase, 1000 TRU and cortisone 3.75 mg. daily	1855/1391	658	4490	2697/2004	1098	5613	1.5	0.6
D	14	1105/800	478	2543	Hyaluronidase, 1000 TRU daily	1355/1000	571	3363	1376/1040	625	3258	2.0	1.8

NOTE: Plasma lipid values in normal rabbits in this laboratory are: Cholesterol, total/esterified—50/35 mg. per 100 ml. Phospholipids—105 mg. per 100 ml. Total lipids—350 mg. per 100 ml. The degree of atherosclerosis is expressed as defined elsewhere [*87*].

and four women. Of these ten persons, seven were given cortisone for five days, two for seven days and one for fourteen days. Daily dosage was 150 mg. in one, 100 mg. in seven, 25 and 50 mg. in one each. The changes in plasma cholesterol and lipoprotein were variable and inconstant. They were in "sharp contrast to predictable changes seen after administration of gonadal hormones." There were, however, striking differences in the duration of administration and the dosages of the two types of hormones. Estinyl was administered in massive doses (1,000 μg. daily) for forty-one days to five months [*21a*, Tables I, II] to survivors of myocardial infarction, whereas cortisone given to normal men and women was used in comparatively small doses for several days.

In contrast to the adrenal cortex, the adrenal medulla appears to exert no significant effect on circulating lipids, although injection of epinephrine appears to provoke a transient ketonuria and ketonemia [*92*]. Increases of serum lipids have been reported by some authors after epinephrine administration [*93*], while others reported a decrease in serum cholesterol, phospholipid and total lipids [*94*]. One may consider that the relatively short duration of all epinephrine effects prevents any pronounced effect on circulating lipids.

In summary, the role of the adrenal cortex in regulating serum lipids and lipoproteins is strongly suggested by recent experimental work in the bilaterally adrenalectomized animal and by the results of hormone administration to normal animals. The latter vary with the animal species. The role of these hormones in man, especially in healthy man, is difficult to evaluate and requires additional studies.

The Pancreas. Knowledge concerning the role of the pancreas in controlling the concentration of circulating lipids is based on the study of pancreatitis and diabetes mellitus in both the experimental animal and in man.

An early observation concerning transient hyperlipemia and hypercholesteremia in experimental pancreatitis in the dog was reported by Binet and Brock in 1929 [*95*]. In our laboratory, studies on the relationship between pancreatitis and serum lipids were performed in rabbits and dogs treated with ethionine, a powerful metabolic competitor of methionine. This substance produces severe changes of hemorrhagic pancreatitis.

Pathological changes in many other internal organs are concomitantly produced, such as fatty metamorphosis of the liver, renal damage and destruction of chief cells of the stomach. Progressive diminution of circulating proteins, lipids, lipoproteins and glycoproteins was seen. There was especially marked reduction of serum gamma globulin, probably a result of extensive suppression of lymphoid tissue. A severe blood coagulation defect was observed which resulted in macroscopic or microscopic hemorrhages in the gastrointestinal tract, the pancreas, spleen, liver, lungs and adrenals [*96,97*]. Thus two fac-

TABLE VII

EFFECT OF EXPERIMENTAL PANCREATITIS, PRODUCED BY PANCREATIC DUCT LIGATION AND INTRADUCTAL STAPHYLOCOCCUS TOXIN INJECTION ("STAPH. T" IN TABLE), ON SERUM LIPIDS OF THE RABBIT. IN THE CONTROL ANIMALS ("SALINE" IN TABLE) LIGATION OF THE DUCT AND INTRADUCTAL INJECTION OF SALINE SOLUTION WAS USED

Serum Components (mg./100 ml.)	Animals (no.)	Substance Injected into Pancreatic Duct	Days after Ligation of Pancreatic Duct + Intraductal Injection										
			0	1	2	3	4	6	8	10	12	14	16
Cholesterol, total/ esterified	19	Staph. T	50/40	54/42	141/69	72/45	53/35	66/47	.....	.....	.....	45/38	.....
	4	Saline	50/35	38/24	70/57	42/36	.....	50/34	.....	41/32	.....	.....	43/31
Phospholipid	19	Staph. T	122	180	340	232	131	162	.....	.....	.....	128	.....
	4	Saline	115	155	144	110	.....	133	.....	133	.....	154	.....
Total lipids	19	Staph. T	263	630	1149	1075	532	430	485	.....	.....	302	402
	4	Saline	260	273	335	260	....	303	303	348	.....	295	295
Blood sugar	19	Staph T	130	125	247	177	.....	150	.....	.....	.....	.....	202
	4	Saline	.....	.....	83	107	.....	91	89	203	105	.....	149
Amylase	19	Staph. T	204	184	462	294	267	196	225	.....	.....	206	169
	4	Saline	202	.....	397	383	.....	249	.....	232	182	.....	209

tors contributed to the genesis of hemorrhagic pancreatitis after ethionine administration. Hemorrhage into the pancreas was part of the general hemorrhagic diathesis produced by this substance; the degeneration and necrosis of the acinar cells was part of its general systemic toxic effect.

Because of the severe pathological changes in many vital organs other than the pancreas and the resulting metabolic disorder, it was thought inadvisable to use ethionine-produced pancreatitis for study of the relationship between the pancreas and circulating lipids. In a search for a more specific "isolated" form of experimental pancreatitis, the instillation of a potent staphylococcus toxin into the ligated pancreatic duct [*98*] proved to be satisfactory [*99*]. The study included thirty-five rabbits and eleven dogs. In nineteen of thirty-five rabbits ligation of the pancreatic duct was followed immediately by intraductal instillation of the staphylococcus vaccine. The remaining sixteen animals served as controls: in four, ligation of the duct and instillation of saline was performed; in nine, only ligation of the duct was used; and in three, ligation was performed first and intraductal instillation of the toxin through a second laparotomy was carried out two weeks later. The full procedure resulted in acute fulminating pancreatitis and produced concomitant lactescence of serum lasting one to four days. (Table VII.) The maximum elevation of serum lipids, observed on the second day, comprised an increase of approximately 200 per cent in total cholesterol and in phospholipid, and 400 per cent in total lipids, mainly caused by elevation of triglycerides. The greater increase of serum triglycerides than of cholesterol and phospholipid in the rabbit is of interest, since a completely different experimental procedure, thyroidectomy, affected the serum lipid partition in a similar way (see section on thyroid). The serum cholesterol and phospholipid returned sooner toward normal levels than did the triglycerides and total lipids. The maximum elevation of the blood sugar and of serum amylase again was noticed on the second postoperative day. The control group, in which ligation of the pancreatic duct was combined with intraductal instillation of saline solution, showed slight elevation of serum lipids, no change in blood sugar but significant elevation of serum amylase. (Table VII.) Similar elevation of serum amylase was seen in rabbits in which, under anesthesia, a simple laparotomy, without any additional manipulation, was performed as well as in a group of nine animals in which the pancreatic duct was ligated without any intraductal instillation. In none of these con-

TABLE VIII

EFFECT OF EXPERIMENTAL PANCREATITIS ON SERUM LIPIDS OF THE DOG*

Serum Components (mg./100 ml.)	Animals (no.)	Substance Injected into Pancreatic Duct	Days after Ligation of Pancreatic Duct + Intraductal Injection							
			0	1	2	3	4	6	9	14
Cholesterol, total/esterified	9	Staph. T	163/126	216/154	204/139	255/180	295/214	143/112	164/119	125/117
	2	Saline	171/138	149/107	172/130	136/118	.....	137/107	154/117	147/116
Phospholipid.....	9	Staph. T	354	368	465	488	469	313	362	339
	2	Saline	340	410	410	410	.....	375	346	414
Total lipids.....	9	Staph. T	680	885	1126	970	1078	729	770	661
	2	Saline	765	813	968	770	.....	810	765	860
Blood sugar.....	9	Staph. T	106	106	69	88	84	89	89	102
	2	Saline	100	67	83	69	.....	90	72	72
Amylase.....	9	Staph. T	330	499	543	935	960	643	638	774
	2	Saline	191	176	134	300	.....	524	496	376

* For details, see Table VII.

trol groups were significant changes of serum lipids seen. In animals in which the toxin was instilled intraductally two weeks after pancreatic duct ligation, severe toxic manifestations were observed within the first twenty-four hours, after which time the moribund animals were sacrificed. It appears, then, that acute pancreatitis produced in otherwise normal rabbits results in characteristic transient elevation of serum lipids affecting mainly triglycerides.

In dogs, experimental pancreatitis produced similar effects. (Fig. 8.) It caused elevation of serum lipids for one to four days but to a lesser degree. (Table VIII.) The maximum elevation in serum cholesterol and phospholipid occurred on the third and fourth postoperative days, whereas that of total lipids and triglycerides was evident on the second day. The elevation of serum amylase was maximal on the fourth day. Ligation of the duct and instillation of saline solution produced only mild elevation of serum phospholipid and total lipids, no changes in blood sugar, but a decided elevation of serum amylase. Thus experiments in the dogs corresponded, in general, with the observations made in the rabbits.

The association of lactescence of serum with pancreatitis was first observed over 100 years ago [*100*]. However, only a small percentage of patients with acute pancreatitis show this association [*101*]. In most instances the lactescence of the serum is of short duration (from one to several days). The problem received considerable attention in recent years in papers and reviews concerning pancreatitis [*102–107*]. Albrink and Klatskin [*101*] observed hyperlipemia and gross lactescence of serum following episodes of acute alcoholism and indicated the possible role of pancreatitis in producing these changes.

Recently, Poulsen [*108*] and Klatskin and Gordon [*109*] stressed the occurrence of relapsing pancreatitis with idiopathic hyperlipemia. Among other pathogenetic possibilities, that of fat emboli in the pancreatic vessels was considered. In patients with idiopathic hyperlipemia and recurrent pancreatitis considerable additional elevation of all serum lipids but especially of triglycerides and total lipids was noted during the attacks and shortly thereafter [*110,111*]. In some instances diabetes mellitus of the mild variety was observed and one may reason that diabetes mellitus may be secondary to associated pancreatitis in patients with idiopathic hyperlipemia even if a definite history of the former is not obtained [*110*].

Some authorities in the field are not convinced of the relationship between idiopathic hyperlipemia and relapsing pancreatitis; because of the rarity of the association, the occurrence of the two disorders in the same person is ascribed to coincidence [*112*]. A survey of the literature reveals many instances of recurrent pancreatitis

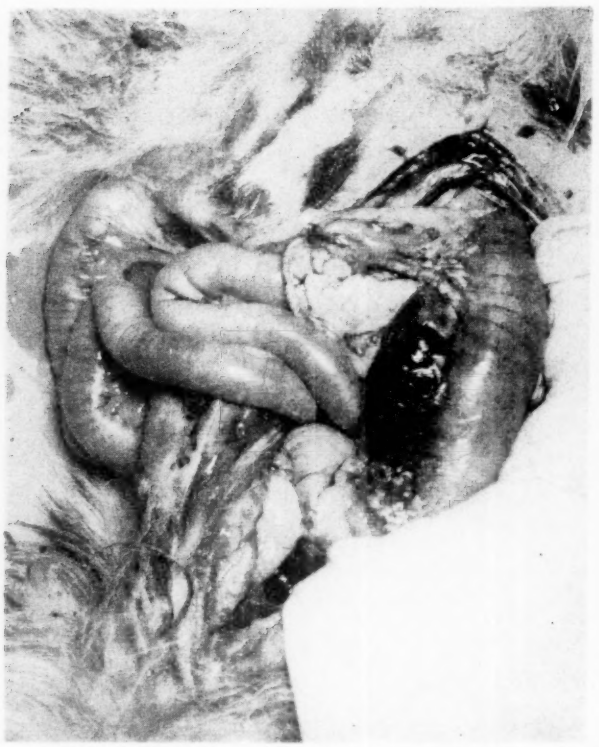


FIG. 8. Dog 664 (June 11, 1956): Pancreatic duct ligation and injection of staphylococcus toxin into the duct. (June 16, 1956): Note severe hemorrhagic pancreatitis and fat necrosis.

in which such an association probably was present although it is often difficult to prove [*113–118*]. In our opinion, the association of idiopathic hyperlipemia with its well established familiohereditary character, with relapsing pancreatitis, which also may be familial, appears to be a real one and not based on chance. Careful serial studies of serum lipids and lipoproteins in patients with relapsing pancreatitis, especially of the hereditary type [*119*], are often missing.

The mechanism by which pancreatitis leads to the alteration of serum lipids is obscure although several possibilities have been considered. Diabetes often is present in experimental and human pancreatitis but it is too mild to explain the elevation of serum lipids. Deficiency of a specific pancreatic hormone regulating lipid metabolism (lipocaic) has been previously considered [*120*]. However, the existence of this hormone is questionable at present [*121,122*]. Certain observations [*123*] point to a possible role of the α-cells of the pancreas and their hormone, glucagon. Destruction of α-cells by cobaltous chloride results in an elevation of serum lipids after twenty-four hours, with gradual return to control levels after seven days, as in experimental pancreatitis. The problem whether or not glucagon is involved in the regulation of lipid metabolism requires extensive additional studies. It is of interest that addition of glucagon resulted in a decrease of fatty acid synthesis in liver slices incubated with C^{14} acetate [*124*]. One must always remember that hormones affecting carbohydrate and/or protein metabolism, such as insulin, may indirectly affect lipid metabolism. Digestion of interlobular pancreatic and/or peripancreatic fat by lipase and release of free fatty acids, as well as embolization of fat at the site of necrosis, have been discussed as possible causes of serum triglyceride elevation [*125*]. The hypercholesteremia and hyperphospholipidemia may be secondary to the triglyceride increase regardless of its origin, since infusion of triglycerides in animals causes hypercholesteremia [*126*].

Convincing evidence of the role of the pancreas in regulating serum lipid levels was obtained in pancreatectomized animals, mainly dogs. Deuel recently published a review of the classical findings in experimental diabetes [*67*]. Only a brief summary will be presented. After extirpation of the pancreas, and with the appearance of ketosis and ketonuria, all lipid fractions of the serum increase considerably. Total lipid concentrations up to 15 per cent have been reported [*127*]. Allen believed that the high serum lipid levels represent a secondary breakdown in fat metabolism, not directly connected with the endocrine function of the pancreas [*128*], while Bloor [*129*] linked these charges directly with loss of the endocrine function of the gland. Treatment of depancreatized dogs with insulin results in a marked fall in serum lipids [*130*]; ketonemia and ketonuria decrease or are completely abolished. These reactions of the depancreatized animal are also affected by the carbohydrate content of the diet, by the carbohydrate reserves of the body, the addition of raw pancreas to the diet, and other factors.

Hyperlipemia is a frequent concomitant of ketosis and acidosis in diabetes in man. The elevation of serum triglycerides results in gross lactescence. Serum cholesterol and phospholipids are often elevated. It occurs in fasting or when, through severe loss of sugar and exhaustion of carbohydrate reserves, the fatty acids derived from fat and protein are not completely utilized. The elevation of serum lipids is usually

explained as "transport-hyperlipemia" although some believe that defective disposal or faulty fat metabolism may be additional important factors [*131*].

Extremely high serum lipid levels occasionally have been observed in patients with diabetes mellitus. The highest reported figure of serum total lipids is 48 per cent [*132*]. This figure was obtained by the centrifugation method for butterfat and may therefore be open to criticism. Other high figures for total serum lipids ranged from 15 to 22 per cent [*133*]. The highest value we have observed was 16 per cent, in a patient with diabetes and idiopathic hyperlipemia [*134*]. The question arose whether or not the extremely high serum lipid levels reported in former years were not caused by a similar association of idiopathic hyperlipemia with diabetes. We are inclined to recognize the association of these two disorders, with a tendency to vascular disease as an interdependent clinical syndrome [*134*]. Patients with this syndrome reveal a remarkable lability of serum lipids in association with hyperglycemia and glycosuria even in the absence of ketonuria. Milder instances of a similar nature might have been observed by Hirsch et al. [*135,136*] whose diabetic patients exhibited marked elevation of esterified fatty acids of the blood in the presence of hyperglycemia. In this connection, recent observations on the relations between non-esterified fatty acids of the plasma (Nefa) and glucose metabolism [*137,138*] deserve consideration.

Complications of diabetes in man may be associated with well defined changes in serum lipids and serum polysaccharides in the absence of ketosis or acidosis [*139*]. Patients with severe retinopathy, hypertension, edema and proteinuria (Kimmelsteil-Wilson syndrome) show a decided elevation of serum lipids and of complex carbohydrates. It is of interest that a group of diabetic patients with early retinopathy but without any evidence of renal involvement present significant differences in comparison with patients with uncomplicated diabetes, and also with non-diabetic patients. These differences include increase in serum triglycerides and total lipids, and in serum glucosamine and total serum polysaccharides, while the serum cholesterol and phospholipid remain within normal limits. One must consider, therefore, that those blood changes perhaps precede the degenerative alteration of the tissue and the deposition of certain protein-lipid and protein-carbohydrate compounds in the retina and in the renal glomerulus. Thus the elevation of these serum components might be pathogenetically related to the development of diabetic retinopathy and glomerulosclerosis.

The Pituitary. Although the role of the pituitary in fat mobilization and in fat metabolism has been extensively studied only inadequate information is available on the role of the "master-gland" in regulating serum lipids. Extracts of the anterior pituitary were found to produce ketosis and fatty infiltration of the liver [*140,141*]. The fat-mobilizing effect of such extracts was studied by Best and Campbell [*142*]. Isotope studies showed that the fatty liver in mice after injection of anterior pituitary extracts is caused by mobilization and migration of fat from the depots to the liver [*143*]. The possibility that the adrenals play a part in this process was suggested by the observation that adrenalectomy suppressed fat mobilization [*74*]. Iversen and Asboe-Hansen [*144*] found that a thyrotrophic extract of the anterior pituitary contained a thyroid-stimulating, an exophthalmogenic and a fat-mobilizing principle. Mobilization of fat from the depots and replacement of the fat by a mucinous hyaluronidase-sensitive polysaccharide was observed after injection of the anterior pituitary extract into intact and thyroidectomized guinea pigs.

Injection of growth hormone produces transient hyperglycemia, perhaps by liberating glucagon into the portal blood [*145*]. Its effect on serum lipids has been only recently studied [*146*]. Hypophysectomy is occasionally associated with hyperlipemia [*147*]. In acromegaly, hyperlipemia and hypercholesteremia have been observed [*148*]; it is believed, however, that these blood changes are related to the diabetes rather than to a direct effect of the pituitary hormone. The effect of ACTH on serum lipids has already been discussed (see section on adrenals).

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Case Reports

Studies of Potassium Secretion in Glomerulonephritis*

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FEW diseases of the kidney are associated with a characteristic pattern of dysfunction. Acute glomerulonephritis, however, is generally consistent in that there is an imbalance between glomerular and tubular function. Usually only glomerular damage is prominent, although elements of tubular dysfunction such as hyposthenuria and deficient excretion of ammonia and acid, may be seen. Rarely, however, does tubular disease predominate. We have recently seen a patient recovering from what appeared to be typical acute glomerulonephritis who had a persistently elevated serum potassium with only minimal azotemia. While hyperkalemia may occur in any type of renal disease when there is extensive deterioration in renal function, the failure to excrete potassium with adequate urine flow is most unusual [*6,9*]. Studies were undertaken to characterize further the retention of potassium evident in this patient, and to evaluate the possibility of a concomitant mineralocorticoid deficiency. The data are interpreted to suggest that such isolated tubular injuries may occur in acute glomerulonephritis, and serve further to emphasize the role of tubular secretion of potassium by the normal and abnormal kidney.

CASE REPORT

This was the first Walter Reed Army Hospital admission of a twenty-one year old white soldier who was transferred from overseas with a diagnosis of glomerulonephritis.

The present illness began on approximately July 7, 1955, with the sudden onset of a moderately severe sore throat, feverishness and generalized malaise. Tonsillitis was noted and the patient was treated with salicylates and a single injection of penicillin. (Table I.) Approximately one week later he again became ill with fever, chilly sensations, a productive cough, nausea and occasional vomiting. On July 26, 1955, he was transferred to a station hospital where pertinent physical findings included a temperature of 98.6°F., blood pressure of 110/76 mm. Hg, inflamed tonsils and rhonchi in the chest. Urinalysis revealed marked albuminuria, hematuria and cylindruria. The hematologic studies demonstrated a white blood cell count of 8,400 per cu. mm.; hemoglobin, 11.7 gm./100 cc.; and a hematocrit of 39 per cent. An x-ray of the chest revealed bilateral pneumonitis. An electrocardiogram was interpreted as normal. The patient was treated with intravenous glucose infusions and penicillin administered intramuscularly. Two days later the sensorium became clouded and he was found to be hypertensive, moderately azotemic and acidotic. On August 1, 1955, an electrocardiogram revealed peaking of the T waves in leads V_2 and V_3. By August 6, 1955, he had gained 11 pounds. Although his sodium intake was then restricted, pitting edema of the lower extremities and periorbital edema developed. Hypertension, albuminuria, cylindruria, including red blood cell casts, azotemia and acidosis continued, and anemia increased. For these reasons he was transferred to Walter Reed Army Hospital. At the time of arrival on September 4, 1955, he was asymptomatic.

The past medical history included hospitalization for two weeks at the age of twelve for backache and gross hematuria which followed heavy lifting. There was no family history suggestive of renal disease. Review of systems revealed no significant symptoms except intermittent spontaneous epistaxis several times a year for many years, and nocturia of one or two times since childhood.

When admitted to Walter Reed Army Hospital the patient appeared pale but in no acute distress. The blood pressure was 160/94 mm. Hg. There was no periorbital edema. The fundi were normal. Inspiratory and expiratory musical rales were heard bilaterally. Examination of the abdomen was normal.

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TABLE 1

EARLY MAJOR FEATURES OF THE PRESENT ILLNESS

Date	Patient's Condition	Signs	Blood Pressure (mm. Hg)	Urine			Blood		
				Specific Gravity	Albumin	Sediment	Hemoglobin (gm. %)	Blood Urea Nitrogen (mg. %)	Carbon Dioxide (vol. %)
		Previous Medical Findings							
3–16–54	Induction	.....	124/70	.....	Negative	.....	....	..	..
9–16–54	Amnesia	.....	118/78	1.021	Negative	Normal	14.0	..	..
10–6–54	Transferred	.....	112/60	1.025	Negative	Normal	14.8	..	..
11–26–54	Vaccination reaction	.....	.....	1.023	Negative	2–3 WBC	12.8	..	..
		Present Illness							
7–7–55	Sore throat, fever, malaise	Tonsillitis	.....	.....	.....	.....	....	..	..
7–16–55	Fever, chills, cough, nausea, vomiting	Pneumonia	.....	.....	.....	.....	....	..	..
7–26–55	Transferred	Pneumonia, tonsillitis, electrocardiogram normal	110/76	1.016	4+	5–10 RBC 30–40 WBC	11.7	..	..
7–28–55	Stuporous	.....	180/100	1.013	2+	5–10 RBC 10–20 WBC RBC casts	....	 42	 40
8–1–55	Alert	Electrocardiogram: peaked T waves	140/93	1.004	2+	RBC,WBC, casts	....	.. 49	.. 44
8–6–55	.....	11 lb. weight gain	150/92	1.010	2+	RBC, WBC, casts	....	45	52
8–15–55	.....	Ankle edema	190/100	.....	.....	18–25 WBC	....	..	..
8–19–55	Transferred	2+ pitting edema feet and ankles	190/110	1.010	4+	740 RBC	9.9	52	..
9–4–55	Transferred to Walter Reed Hospital	.....	.....	.....	.....	.....	....	..	..

There was no costovertebral angle tenderness. Minimal ankle edema was present.

Admission urinalysis revealed, pH, 5.0; specific gravity, 1.008; albumin, 2 plus; the sediment contained approximately 200 red blood cells and 5 to 8 white blood cells per high power field and 5 to 10 granular casts per low power field. White blood cell count was 9,000 per cu. mm. with a normal differential count; hemoglobin, 11.4 gm./100 cc.; hematocrit, 32 per cent; corrected erythrocyte sedimentation rate, 27 mm./hour. He was offered a diet containing 14 mEq. sodium and 50 gm. protein, and at least 2,500 cc. of fluid was taken daily. Chemical studies of the blood during the first week gave the following results: Blood urea nitrogen, 33 mg./100 cc.; non-protein nitrogen 48 mg./100 cc.; carbon dioxide, 18 mEq./L.; chloride, 108 mEq./L.; inorganic phosphorus, 7.0 mg./100 cc.; calcium, 10.4 mg./100 cc.; albumin, 3.1 gm./100 cc.; globulin, 4.1 gm./100 cc.; uric acid, 7.2 mg./100 cc.; glucose, 80 mg./100 cc.; and cholesterol, 208 mg./100 cc. Urinary protein loss averaged approximately 1.5 gm./L. with an average urine volume of 2,500 cc. No Bence Jones protein was present. Routine cultures of urine were negative, as were cultures for Mycobacterium tuberculosis. Several L.E. cell preparations were negative. No group A streptococci were isolated on throat culture. The antistreptolysin O titer was above 625 units. The x-ray of the chest was within normal limits. On the twelfth hospital day serum sodium was 138 mEq./L. serum potassium, 7.7 mEq./L., and blood urea nitrogen, 51 mg./100 cc. An electrocardiogram at this time revealed marked peaking of the T waves in leads V_2–V_3. (Fig. 1.) Sodium restriction was discontinued, and the patient was given a diet containing 40 mEq. potassium and approximately 50 gm. of protein. Within four days the blood urea nitrogen fell to levels of 25 to 30 mg./100 cc.; however, the serum potassium remained elevated (usually 6.5 to 7.0 mEq./L.). The twenty-four-hour urinary potassium excretion approximated the calculated intake. After thirty-two days on this diet, the serum potassium remained unchanged and the electrocardiographic abnormalities persisted.

The history was considered compatible with glomerulonephritis, probably acute, although the possibility of an earlier childhood episode of nephritis was considered. There was a striking disparity between retention of urea and potassium. The urine was acid (pH 5.0) and there was a systemic metabolic acidosis. The patient was transferred to the Metabolic Ward for further studies.

The patient was given a liquid diet containing 20 mEq. of potassium, 100 mEq. of sodium, 60 gm. of

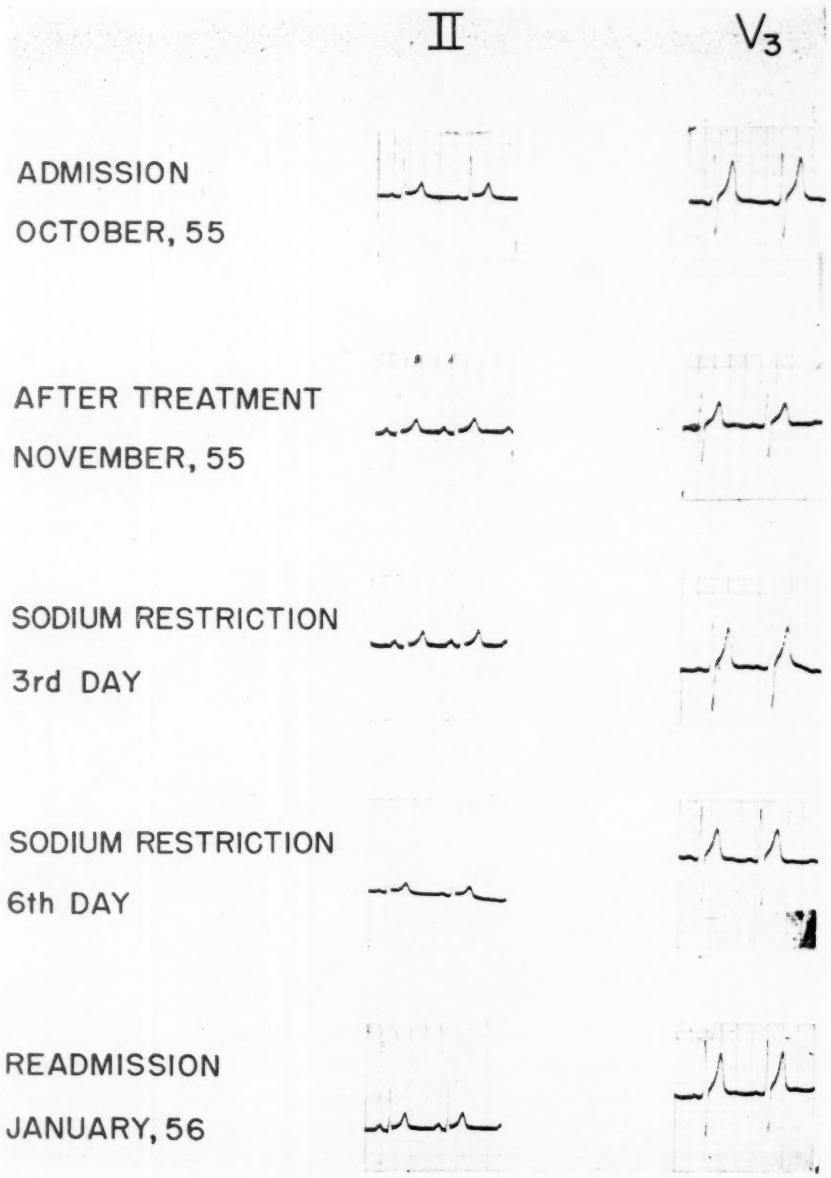


FIG. 1.

protein, and approximately 3,000 calories daily. The blood chemical values were as follows: sodium, 135 to 147 mEq./L.; potassium, 6.0 to 7.0 mEq./L.; chloride, 108 to 117 mEq./L.; carbon dioxide, 16.5 to 18.0 mEq./L.; blood pH, 7.2 to 7.3; calcium, 10.0 to 11.0 mg./100 cc.; inorganic phosphorus, 5.7 to 6.9 mg./100 cc.; blood urea nitrogen, 23 to 32 mg./100 cc.; non-protein nitrogen, 48 mg./100 cc.; and creatinine 1.8 to 2.0 mg./100 cc.

The daily urine output ranged from 1.8 to 4.0 L. The specific gravity varied from 1.004 to 1.011. Total solute, as measured by freezing point depression, was 133 to 409 mOsm./kg. The urine was consistently acid (pH 4.8 to 5.4). The concentration of ammonia in the urine varied from 3.0 to 9.7 mM/L. and the titratable acidity was 15 to 25 mEq./L. The concentration of potassium in the twenty-four-hour urine specimens was usually 9 to 15 mEq./L., but during some shorter periods the U/P ratio was as low as 0.4. Various studies were directed toward determining whether these abnormalities were the result of a primary renal defect or were secondary to insufficiency of salt-regulating steroids.

Renal function studies were performed. Endogenous creatinine clearance (C_{cr}) over twenty-four-hour periods ranged from 45 to 50 cc./minute. Inulin clearance (C_{inulin}) averaged 27 cc./minute. Para-aminohippuric acid clearance (C_{PAH}) averaged 312 cc./minute. These studies were repeated after correction of the acidosis, and again two months later.

(Table II.) Tests of the ability to concentrate the urine were also abnormal, although a gradual improvement was noted. (Table III.)

The ability of the kidney to respond to various stimuli which are known to enhance potassium excretion by the normal kidney was then evaluated. (Table IV.) First, the effect of hyperventilation was examined. Thirty respirations per minute for a thirty-minute period caused mild tetany and light-headedness. The serum carbon dioxide decreased from 19.9 mEq./L. to 17.6 mEq./L., and the blood pH rose from 7.21 to 7.38. Although the urine pH rose slightly, it remained acid. Potassium excretion increased 440 per cent and there was a decrease in hydrogen ion excretion. Several days later the effect of carbonic anhydrase inhibition was examined. After several control periods, 10 mg./kg. of diamox® was ingested. The urine pH rose to 6.46 during the second hour. Despite a fall in creatinine clearance, potassium excretion increased 380 per cent. Finally, an alkaline load was administered by giving 5.0 gm. of sodium bicarbonate orally every thirty minutes. After a four-hour period the urine remained acid (pH 5.93), and therefore 200 cc. of 7.5 per cent sodium bicarbonate solution was administered intravenously. Severe alkalosis with signs of marked tetany developed. The urine became alkaline (pH 7.68) and potassium excretion increased 250 per cent. There was no increase in potassium excretion prior to the intravenous administration of sodium bicarbonate. Thus, in response to three types of stimulation potassium excretion was increased. However, at no time did more than 25 per cent of the filtered load of potassium appear in the urine. Ammonia excretion averaged 6.9 μM/minute (range 2.5 to 16.0 μM/minute), and the urine pH varied from 4.90 to 5.06 during the control periods.

Table II
RENAL CLEARANCE STUDIES

Date	Serum CO_2 (mEq./L.)	Blood pH	Ccr (cc./min.)	GFR Cin (cc./min.)	RPF CPAH (cc./min.)	Filtration Fraction $\frac{C_{in}}{C_{PAH}}$
11–55	19.3	7.16	60.9	27.2	311.4	0.12
	34.2	7.51	61.3	37.6	335.7	0.12
1–56	24.8	....	111.3	48.2	424.1	0.11
4–56	25.2	....	121.2	....	.....	....

NOTE: Ccr Creatinine clearance.
Cin Inulin clearance.
CPAH Para-amino-hippuric acid clearance.

Table III
URINE CONCENTRATION TESTS

Date	Procedure	$D\frac{15°}{15°}$	mOsm./kg. Urine
11–55	10 units pitressin®	1.010	468
1–56	Overnight dehydration	1.015	545
	10 units pitressin	1.020	623
4–56	Overnight dehydration	1.024	786
	10 units pitressin	1.024	740

NOTE: Several one-hour specimens were collected in each study prior to breakfast. Only the maximum values are given.

Although the measured daily loss of potassium approximated dietary intake, serum levels gradually fell, and after the second week ranged from 4.6 to 5.2 mEq./L. A deficiency of salt-regulating hormones was considered, either as a primary deficiency of aldosterone or as a secondary failure of the damaged kidney to respond to salt-regulating adrenal hormones. There were no symptoms or signs of hypoadrenalism or hypopituitarism. Glucose and insulin tolerance tests were normal. Twenty-four hour thyroidal radioactive iodine uptake was 21 per cent. Urinary excretion of follicle-stimulating hormone was (less than)

Table IV
THE EFFECT OF VARIOUS STIMULI ON POTASSIUM EXCRETION

Procedure	Rate μEq./K (min.)	C_K (cc./min.)	$\frac{C_K}{C_{cr}}$	$\frac{U}{P}K$
Control	7	0.9	.02	0.4
Hyperventilation (period 3)	28	4.2	.09	1.3
Control	14	1.7	.04	0.5
Diamox, 10 mg./kg. (period 5)	77	12.8	.23	2.2
Control	20	3.0	.06	0.8
Oral $NaHCO_3$, 35 mg. (period 7)	23	2.7	.08	3.1
Intravenous $NaHCO_3$, 15 gm. (period 9)	84	10.4	.17	4.6

NOTE: Only the maximal effect is given. All periods are twenty to thirty minutes in duration. The control values are the average of the first two periods.

6 mouse units per twenty-four hours. Diuresis occurred promptly following an oral load of water (20 cc./kg.). ACTH, when administered intravenously over an eight-hour period on each of five days, showed a normal response. (Table v.) Desoxycorticosterone acetate (5.0 mg. percorten,® aqueous) was administered intramuscularly twice daily over a forty-eight-hour period. The response was qualitatively normal. (Table vi.)

TABLE V
RESPONSE TO ADRENOCORTICAL HORMONE

Day	Procedure	Urine 17-OH (mg./24 hr.)	Salivary Na/K	Urinary Na/K
0	Control	1.7	2.3	5.3
1	ACTH	13.5	1.3	...
2	ACTH	17.2	1.2	3.0
3	ACTH	13.6	.8	3.7
4	ACTH	23.2	...	2.3
5	ACTH	20.7	...	2.6

NOTE: Twenty units of ACTH were administered intravenously during an eight-hour period for each of five consecutive days.

The daily dietary sodium was then decreased from 100 mEq. to 10 mEq., and the potassium was increased from 20 mEq. to 40 mEq. in order to assess endogenous aldosterone production. Urinary excretion of sodium decreased, and by the sixth day the patient was in sodium balance. (Table vii.) Aldosterone excretion increased tenfold during this period. At the onset of sodium deprivation, the serum potassium was 4.7 mEq./L., and the electrocardiogram was normal. Progressive hyperkalemia developed, reaching a peak of 7.6 mEq./L. on the sixth day. This was associated with peaking and tenting of the T waves. (Fig. 1.) Thereafter the level of serum potassium fell slightly. During the period of sodium restriction there was no change in the twenty-four-hour endogenous creatinine clearance (55 to 65 cc./minute). The blood urea nitrogen rose progressively during the seven days of sodium restriction and for three days thereafter (20 mg./100 cc. to 44 mg./100 cc.), and returned toward normal during the subsequent weeks. With resumption of a regular diet serum potassium gradually decreased, although the diet contained an estimated 100 mEq. of potassium as well as 100 mEq. of sodium daily.

The patient was given one month's convalescent leave from the hospital following completion of the metabolic studies. No dietary restrictions were suggested during this period. Upon his return in January he was asymptomatic and did not appear ill. The blood pressure was 152/82 mm. Hg. Physical examination revealed no other abnormalities, except for musical rales in the chest. Urinalysis revealed pH 5.5, specific gravity 1.010, albumin trace; the sediment contained 50 to 100 red blood cells and 5 to 10 white blood cells per high power field, red blood cell casts and granular casts. Routine cultures of urine were negative. The hemoglobin was 13.2 gm./100 cc. and the hematocrit 40 per cent. The blood chemical values were as follows: sodium, 143 to 135 mEq./L.; potassium, 6.4 to 5.8 mEq./L.; chloride, 114 to 106 mEq./L.; carbon dioxide, 26.9 to 24.0 mM/L.; blood urea nitrogen, 32 to 16 mg./100 cc.; inorganic phosphorus, 4.5 mg./100 cc.; calcium, 11.2 mg./100 cc.; serum albumin, 4.0 gm./100 cc.; and serum globulin 2.7 gm./100 cc. The serum potassium was highest upon readmission and fell progressively during the seventeen days of further observation to 4.1 mEq./L. Improvement in all his abnormal laboratory findings, including renal clearances, was noted. (Table ii.)

TABLE VI
RESPONSE TO DESOXYCORTICOSTERONE

Date	Procedure	Urine		Na/K
		Na (mEq./L.)	K (mEq./L.)	
11–1–55	Control	40.7	8.7	4.7
11–2–55	Control	28.0	5.1	5.5
11–3–55	DOCA	16.5	14.3	1.2
11–4–55	DOCA	31.2	17.9	1.7
11–5–55	Recovery	35.0	9.0	3.9
11–6–55	Recovery	54.0	11.6	4.7

NOTE: Five mg. of DOCA were given at twelve-hour intervals for a two-day period.

TABLE VII
RESPONSE TO SODIUM DEPRIVATION

Day	Diet (mEq. Na)	Urine		Aldosterone (μg./24 hr.)
		Na (mEq./L.)	K (mEq./L.)	
1 (11–17–55)	10	67.7	12.4	..
2	10	54.1	15.1	..
3	10	43.1	30.3	8
4	10	28.3	24.4	11
5	10	17.2	8.5	30
6	10	9.0	12.8	34
7	10	4.8	11.4	79

NOTE: One gm. of diamox was administered daily on the sixth and seventh days in an attempt to aggravate sodium loss.

In March, while on leave, the patient again became

acutely ill with fever and a sore throat. Upon his return forty-eight hours later he was febrile and appeared acutely ill. His blood pressure was 126/70 mm. Hg and an erythema of the soft palate and oropharynx was noted. Throat cultures revealed only normal flora, and antistreptolysin titer measured later was normal. Gross hematuria was noted and the sediment contained numerous red cell casts. With penicillin therapy the patient became afebrile within eighteen hours, although microscopic hematuria continued. The urine pH was 6.2 to 6.9. Blood chemistry values included blood urea nitrogen, 21 mg./100 cc.; cholesterol, 230 mg./100 cc.; and serum potassium, 5.0 to 5.4 mEq./L. During the next month the urinary sediment slowly improved. Potassium excretion was consistently more than 50 μEq./minute. Maximal urinary concentration further increased. The capacity to excrete ammonia remained limited; after 150 mEq. ammonium chloride per day for a three-day period only 6 to 8 μM/minute were excreted with urine pH below 5.5.

When the patient's condition was re-evaluated nine months after the apparent onset of his illness, he felt and appeared entirely well. Blood pressure had returned to normal levels. Blood chemistry values were normal (serum potassium, 4.0 to 4.5 mEq./L.). There was neither azotemia nor anemia. Sedimentation rate was normal. Minimal albuminuria and cylindruria persisted. All measured parameters of renal function, except ammonia production, showed progressive and continued improvement.

COMMENTS

The ability of the kidney to excrete potassium is usually considered to be one of the last functions to be destroyed by disease [*6,9*]. So long as the volume of the urine is not diminished excess potassium usually is cleared from the plasma, despite the retention of other substances in abnormal amounts [*10,15*]. Although many features of this patient's illness seemed to indicate an acute renal injury, the infrequency of hyperkalemia in the usual case of nonoliguric acute or subacute glomerulonephritis prompted consideration of some other cause for the abnormality in potassium metabolism.

While the many factors involved in potassium homeostasis are not completely defined, primary regulation of potassium balance is probably under both remote endocrine and direct renal control [*1*]. A persistently diminished excretory rate in the presence of elevated serum level could be a result of an inadequate stimulus for excretion, an excessive stimulus to retention or failure of the kidney to respond to normal stimuli for potassium excretion.

A deficiency in adrenal mineralo-corticoid secretion was considered. There was neither clinical nor biochemical evidence of adrenal insufficiency; during drastic sodium restriction the urinary excretion of aldosterone increased, and daily sodium excretion rapidly fell.

Similarly, an unrecognized depletion of potassium could have stimulated potassium retention [*3*]. The persistence of hyperkalemia, while not implying an increased body content of potassium [*14*], is not compatible, however, with simple potassium deficiency, and suggests a failure of renal excretion. Neither does the low rate of potassium excretion necessarily indicate depletion, and prolonged balance observation on diets both low and normal in potassium content failed to confirm any sizable deficit. Thus, in the absence of paraphysiologic intake of potassium, a deficiency of renal excretion was confirmed. The two major aberrations in renal function which seemed possible were primary renal failure related to a critical diminution in glomerular filtration or an isolated tubular dysfunction.

It is not likely that the reduction in filtration rate evident in this patient can explain the failure of potassium excretion with continued hyperkalemia. Unlike the excretion of urea, creatinine and probably phosphate, the excretion of potassium is largely independent of the filtered load [*1*]. In chronic renal insufficiency, clearance ratios of potassium/inulin are frequently greater than 1.0, suggesting that the ability to secrete potassium may be preserved long after glomerular filtration is severely reduced [*11,15*]. This is manifest clinically by the infrequency of hyperkalemia even in the presence of azotemia [*10*]. In the present study the increase in serum potassium precipitated by drastic sodium restriction could have been the result of a decrease in glomerular filtration rate, with a resultant decrease in the load of filtered potassium. However, as measured by creatinine clearance, changes in filtration rate were minimal, and since serum potassium increased by 80 per cent, it is more likely that the filtered load of potassium actually increased. Thus it would appear that this patient's impaired ability to excrete potassium cannot be ascribed to reduced filtration resulting from reduced effective renal mass.

It is currently believed that most of the potassium in the urine derives from tubular secretion, and that the filtered potassium is reabsorbed [*2,18*]. An absolute limitation in the tubular

secretory capacity or a relative insensitivity of these mechanisms to regulatory stimuli would cause diminished excretion of potassium as seen in this patient. Following the administration of diamox or sodium bicarbonate, or the induction of hyperventilation, the per cent increases in potassium excretion were normal [*7,8,12,19*], but the absolute increased potassium losses were minor, and serum levels were little affected. The renal capacity to respond to mineralo-corticoids, however, as seen in response to DOCA and ACTH, was not impaired. Thus, some increase in potassium excretion was possible. The data do not allow differentiation between a limit imposed by absolute capacity from a relative insensitivity of tubules to stimuli which generally increase potassium excretion by the normal kidney.

If these significant increases in potassium excretion could be induced by acute stimulation, why was not the chronic hyperkalemia, which is usually considered a major stimulus to potassium secretion [*1*], self limiting? Furthermore, the persistence of hyperkalemia despite the demonstrable renal potential to augment potassium excretion in response to mineralo-corticoids suggests that increased level of potassium in the serum was not an important stimulus to aldosterone production.

Although a number of acute stimuli may temporarily alter potassium excretion independent of either body stores or serum level, i. e., acidosis, alkalosis, sodium or osmotic loading, it is not likely that such stimuli are ordinarily factors in maintaining potassium balance. Thus the persistence of hyperkalemia with reduced excretion in this patient is considered to be a quantitative deficiency in potassium secretion manifested by an insensitivity to the level of potassium in the serum, and a reduced sensitivity or capability in response to other stimuli. As the secretion of potassium is thought to be in part dependent on the availability of sodium ions for exchange [*1,2*], one may explain the observed effect of dietary sodium restriction independently of changes in filtration rate. Increased reabsorption of sodium, induced by the low salt diet, presumably at a site proximal to that of potassium secretion, might be expected to diminish further an already low secretory rate of potassium. The finding of U/P ratios of potassium less than 1.0 with relatively low urine flow rates logically confirms the concept of dependence of urinary potassium on secretion rather than suggesting that a superlative reabsorption would be induced by a disease process.

Ammonia excretion was also grossly deficient when correlated with the acidity of the urine and reduced serum pH. No increase in urinary ammonia was provoked by the restriction of sodium or, subsequently, by the administration of ammonium chloride. In the latter instance considerable recovery in concentrating ability and potassium secretion was already in evidence. The persistently acid urine relatively free of ammonia implies failure of intracellular production, if the excretion of ammonia is ascribed to passive diffusion conditioned by acidification of the urine [*16*]. Furthermore, deficient ammonia production suggests a potential inefficiency in the conservation of other cations, and may have been a factor in the induction of the metabolic acidosis in the absence of severe azotemia. The apparent dissociation of the capacity for urine acidification from potassium secretion is not entirely compatible with the concept that both hydrogen and potassium are secreted at the same tubular site, although their reciprocal relationship was evident [*2*].

As a converse to the abnormalities noted in this patient, excessive potassium loss rarely may be seen as a feature of many types of renal disease [*5,13,17*]. This has been construed as a disorder of the renal tubule. It is difficult to reconcile both deficient excretion and excessive excretion of potassium, as manifestations of tubular disease. It is currently believed that substances which are excreted in excess as a result of tubular insufficiency, i.e., amino acids, glucose, phosphorus and possibly albumin, owe their abundance in the urine to faulty reabsorption [*4,13*]. While elements of reabsorptive failure may appear clear-cut in these instances, it is not necessary to associate a coincident increased potassium loss as evidence of a similar tubular dysfunction. It seems feasible that the renal loss of potassium, when associated with other tubular reabsorptive deficiencies, may be due to stimulated secretion. The potassium wasting seen rarely in chronic renal disease may thus be the secondary response of an intact secretory mechanism to other tubular defects involving urine acidification and inorganic cation conservation.

SUMMARY

1. A patient has been studied with acute renal disease best characterized as glomerulonephritis but associated with prolonged hyper-

kalemia and the inability to form ammonia in the presence of an only moderately reduced glomerular filtration rate.

2. The basic defect seemed to be one of specific impairment of the potassium secretory mechanism. The ability to excrete potassium was gradually regained over a period of nine months.

3. The exaggerated potassium excretion observed in a number of renal tubular defects or associated with chronic renal insufficiency may represent increased tubular secretion of potassium rather than a reabsorptive failure.

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"Cor Triatriatum"*

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The clinical, roentgenologic, electrocardiographic and postmortem findings in a two year old white girl with "cor triatriatum" are presented, together with the data obtained on cardiac catheterization. An anomalous septum with a small opening divided the left atrium into two chambers, one communicating with the pulmonary veins and one with the left ventricle. The functional similarity between this condition and mitral stenosis is discussed, the possibility of suspecting the abnormality on the basis of an extremely elevated pulmonary "capillary" pressure is emphasized, and the feasibility of surgical correction is suggested.

Cor triatriatum is a rare entity. In a recent review of the world's literature only twenty-two cases were found [*1*]. While this condition has never been diagnosed antemortem, the present case and the one previously reported case in which cardiac catheterization was performed indicate that such studies might at least suggest the diagnosis.

CASE REPORT

G. A. S., a seven months old white female infant was first seen in the emergency room of the North Carolina Baptist Hospital in the fall of 1952 because of an upper respiratory infection. The heart was thought to be normal at that time. Two years later she was admitted to this hospital with chief complaints of "feeding difficulties and heart trouble." The feeding difficulties resulted from the accidental ingestion of lye solution four to five months previously.

The mother stated that the child had had recurrent attacks of dyspnea, with cyanosis of the lips and extremities, during the previous year. With the first attack, which occurred on a hot summer afternoon, the patient was unconscious for about a minute. She had two more attacks on the same day and continued to have one or two similar episodes each day for two weeks. In October, 1953, a roentgenogram of the chest was made, and the mother was told that the child had "a hole in the right side of the heart." Digitalis therapy was begun then and continued until her first admission to this hospital. During the winter of 1953 to 1954 the child had many colds and earaches; sulfadiazine therapy was begun in February, 1954, and was administered daily for a period of two months. The child continued to have an attack of dyspnea and cyanosis about once a month. In the spring of 1954 she accidentally ingested a lye solution, and three weeks later she began to have bleeding from the nose and mouth, accompanied by fever. She was hospitalized elsewhere and treated with a blood transfusion and intravenous fluids. From that time until her admission here she ate very poorly, taking only milk and crackers.

Physical examination on admission showed a temperature of 98.0°F., a pulse rate of 88, a respiratory rate of 30, and a blood pressure of 95/60 mm. Hg. The child weighed 17 pounds, 11 ounces (3 percentile for one year) and was 33 inches tall (25 percentile for two years). She was a poorly developed, poorly nourished, fretful child who appeared chronically ill. No cyanosis, clubbing or edema was present. The skin was dry, warm and of fair turgor. The lungs were clear to percussion and auscultation. The sternum was abnormally prominent, and the anteroposterior diameter of the chest was increased. There was no thrill. The cardiac dullness extended 2 cm. to the right of the sternum and 3 cm. to the left of the left midclavicular line. The rhythm was regular. The pulmonic second sound was snapping in quality and was much louder than the aortic second sound. A grade 2 systolic murmur was heard along the left lower border of the sternum. The liver was palpated 2 cm. below the right costal margin. The femoral and dorsalis pedis arterial pulsations were palpable bilaterally.

A complete blood count showed a hemoglobin of 13.5 gm. per cent, 5,400,000 erythroctyes and 16,000 leukocytes per cu. mm., with 61 per cent segmented neutrophils, 6 per cent non-segmented neutrophils, 2 per cent eosinophils, 28 per cent lymphocytes and 3 per cent monocytes; platelets were adequate. The sedimentation rate was 2 mm. in the first hour. The volume of packed red cells was 43 per cent, the mean corpuscular volume 80 cubic microns, the mean corpuscular hemoglobin concentration 31 gm. per cent. Examination of the blood smear revealed microcytosis

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and hypochromia. Examination of the urine revealed no significant abnormalities. Serologic tests for syphilis were negative.

An electrocardiogram (Fig. 1) revealed sinus tachycardia, right axis deviation and right ventricular hypertrophy. Abnormal P waves were also noted.

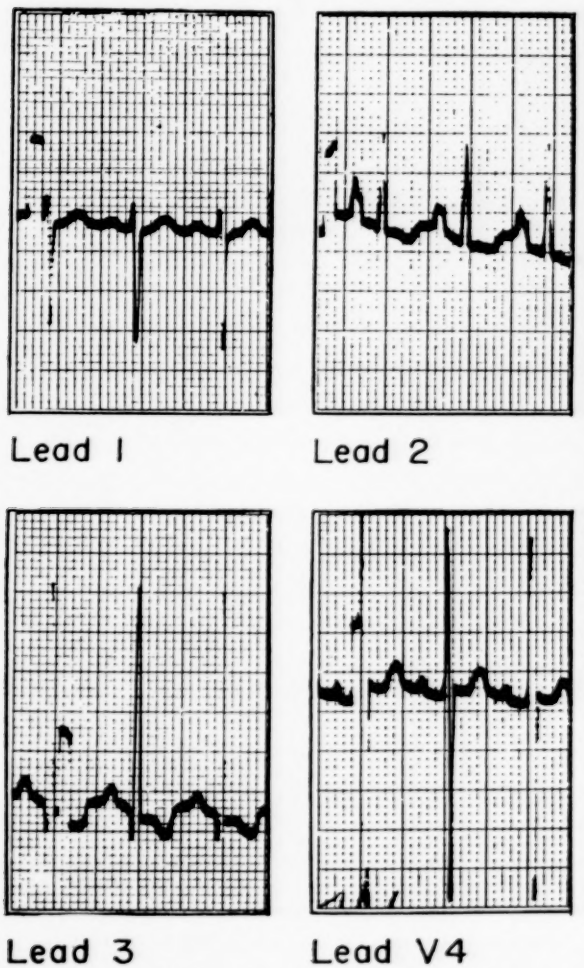


FIG. 1. Patient G. A. S. The electrocardiogram showing right ventricular hypertrophy, and tall, notched P waves in lead II.

Roentgenologic examination of the chest with barium swallow showed narrowing of the middle third of the esophagus. The angle of the carina was thought to be displaced upward. The heart was enlarged and globular in shape; the cardiothoracic ratio was 9:15.3 cm. The shape was interpreted as indicating hypertrophy of the right ventricle. No hilar pulsations were seen but the density of both hilar regions was increased. (Fig. 2.)

Prior to cardiac catheterization, the most likely diagnosis was thought to be either tetralogy of Fallot or pulmonary stenosis associated with an interatrial septal defect. Cardiac catheterization was performed on the patient's fourteenth hospital day. Pressures were recorded by means of Statham pressure transducers, a 2,000 cycle amplifier, and a Sanborn DC amplifier and multiple channel direct-writing oscillograph. The apparatus was calibrated with a mercury manometer to permit direct reading of pressure in millimeters of mercury. The zero point for all pressures was 10 cm. anterior to the skin of the back.* Mean pressures were determined by planimetric analysis of the pressure curves recorded. Blood oxygen contents and oxygen capacity were measured by Van Slyke analysis. Oxygen consumption was not measured. The data are recorded in Table I.

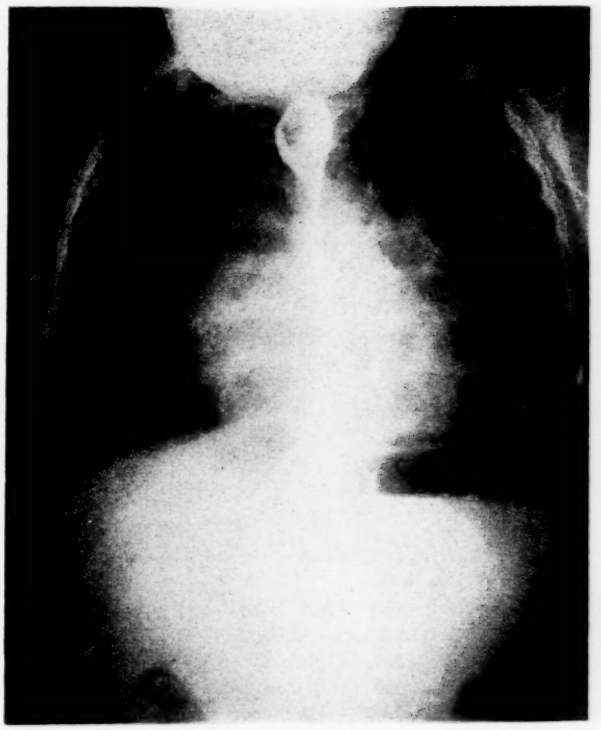


FIG. 2. Patient G. A. S. A roentgenogram of the chest, with barium swallow.

The blood oxygen contents showed no evidence of a left-to-right shunt. The low systemic arterial oxygen saturation indicated either a right-to-left shunt or impairment of oxygenation in the lungs. Since the systolic pressures of both the pulmonary artery and the right ventricle were greater than the systemic arterial pressure, a shunt, if present, would have to be in a right-to-left direction. The low arterial oxygen saturation was compatible with such a shunt. The pulmonary "capillary" pressure, which is considered to be a reflection of left atrial pressure [*2,3*], also was elevated markedly (30 mm. Hg).

A diagnosis of the Eisenmenger's complex or pulmonary vascular disease was considered but neither would explain the extremely elevated pulmonary capillary pressure.

* Since this patient's anteroposterior chest diameter was only 13 cm., this zero point is high; for the sake of consistency, it was employed. Thus the actual values are slightly higher than those recorded.



FIG. 3. "Triatrial" heart (L.A. = distal left atrial chamber; P.V.A. = proximal left atrial chamber; P.V. = pulmonary veins). The probe to the left passes through the orifice in the anomalous septum. The three probes to the right are in the orifices of three of the four pulmonary veins. The dilated and thickened right ventricle is at the lower right.

During the patient's sixteen days of hospitalization esophageal dilatation was carried out by members of the otolaryngology staff. On one occasion the patient became cyanotic following the dilating procedure. The patient was discharged on October 1, 1954, without medication, to be followed up in the outpatient clinic.

On the day after discharge the patient began to vomit her feedings, and the mother noted labored breathing which became progressively worse during the next two days. On the third day after discharge, swelling of the eyes, hands and feet was noted, and the patient had a bout of cyanosis following an episode of severe vomiting which lasted five minutes. She was brought to the hospital and readmitted on October 4, 1954.

On physical examination the breathing was labored and grunting, with a rate of 48–52; the pulse was 140, the temperature 100°F., the blood pressure 80/40 mm. Hg. The alae nasi flared with each inspiration. The neck veins were distended, and occasional moist inspiratory rales were heard in the base of the right lung. A systolic thrill was noted over the precordium. No change in heart size or in the murmur noted on the previous admission was detected. The abdomen was distended, and the liver edge was palpated 4 cm. below the right costal margin. There was moderate pitting edema of the hands and lower extremities. A chest roentgenogram showed no definite change since the previous examination.

Digitalis and morphine were administered, and the child was placed in an oxygen tent. The dyspnea became progressively worse, however, and the patient died fifteen hours after admission.

At postmortem examination the pericardial cavity contained 30 cc. of cloudy amber fluid, and the heart weighed 130 gm. (The average weight for this age is 57.5 gm.) The venae cavae opened into the right atrium in the usual manner; the foramen ovale was closed, and the right atrium was moderately dilated. The myocardium was thickened, measuring 0.7 cm. at a point just above the base of the posterior papillary muscle. The circumferences of the tricuspid and pulmonary valve rings were 7.0 and 4.2 cm., respectively. The valves, endocardium, myocardium and epicardium of the right side of the heart were otherwise within normal limits.

TABLE I
PHYSIOLOGIC FINDINGS IN PATIENT G. A. S.

Area	Oxygen (cc./100 cc.)	Oxygen, Per cent Saturation	Pressures (mm. Hg)	
			Systolic/Diastolic	Mean
Pulmonary capillary	.....	..	.....	30
Pulmonary artery	7.78	57	125/72	98
Right ventricle (left lateral)	8.08	59	122/2	65
Right ventricle (apex)	7.21	53	.....	..
Right atrium (low)	8.70	64	.....	3
Right atrium (high)	7.49	55	.....	..
Superior vena cava	9.24	68	.....	2
Femoral artery	11.08	82	.....	..
Brachial artery	.....	..	95/60*	..
Oxygen capacity	13.75	..	.....	..

* Measured clinically with the sphygmomanometer.

The pulmonary artery was slightly dilated, and its wall slightly thickened. Each of the four pulmonary veins opened separately into a somewhat ovoid chamber, which was separated from the left atrium proper by an opaque, thin, nearly complete septum. (Fig. 3.) The only communication between the anomalous chamber and the left atrium was an eccentric, roughly circular orifice in the septum, 0.3 cm. in diameter. The external surfaces of the anomalous chamber and the left atrium proper were continuous. The left auricle showed slight dilatation and communicated with the left atrium proper, while the fossa ovalis was in the medial wall of the anomalous chamber. Except for its small size, the principal portion of the left atrium proper revealed no abnormalities. The circumferences of the mitral and aortic valve rings were 5.7 and 2.9 cm., respectively, and the myocardium of the left ventricle was 0.7 cm. thick at a point just above the base of the anterior papillary muscle. The mitral and aortic valves, and the endocardium, myocardium and epicardium of the left ventricle were otherwise normal. The aorta and its major branches had a normal appearance, and the ductus arteriosus was closed.

Microscopically, the myocardial fibers of the right ventricle showed hypertrophy. The abnormal septum was composed of a few fibers of cardiac muscle interposed between two layers of collagenous connective tissue. The latter contained a few elastic fibers and was covered on each surface by a single layer of endothelial cells. The remainder of the heart was without evident lesions.

The right and left pleural cavities contained, respectively, 150 and 50 cc. of cloudy, amber fluid. The right lung weighed 230 gm., the left lung 210 gm. (The average weights for this age are 88 and 76 gm. [*4*].) The lungs displayed decreased crepitation and floated poorly in water. Their external surfaces were pink-gray in color, mottled with red and purple. The sectioned surface of the left lung was red and that of the right was pink mottled with red.

Microscopically, many of the alveolar capillaries were dilated and tortuous, frequently forming aneurysmal protrusions into the alveolar spaces. The muscular arteries showed concentrically thickened media with slightly narrowed lumens. A moderate amount of fibrous tissue was present between the endothelium and the internal elastic lamina of the larger arteries. The alveoli contained many extravasated erythrocytes and, in some sections, collections of edema fluid. A few of the alveolar walls were torn, and their free ends presented a club-shaped appearance. The alveoli and bronchioles contained many macrophages, in which the presence of intracytoplasmic hemosiderin was confirmed by the potassium ferrocyanide reaction.

No other congenital anomalies were present in the organs or tissues examined. The central lobular portions of the hepatic parenchyma were markedly hyperemic, and the kidneys showed minimal hyperemia. An additional finding was stenosis of the esophagus, most pronounced near the junction of its middle and lower thirds.

COMMENTS

Although several theories have been advanced, the embryologic basis for this anomaly is not established [*5*]. The most widely accepted hypothesis at present is that the septum represents a defect in the development of the common pulmonary vein but this theory fails to explain the presence of the fossa ovale in the medial wall of the anomalous chamber. No further attempt will be made here to discuss this aspect of the problem.

In retrospect it is easy to explain the clinical picture and the catheterization data in this patient on the basis of the postmortem findings. The basic abnormality was a partial obstruction to the flow of blood from the lungs to the left ventricle; an abnormal septum divided the left atrium completely except for an opening which was less than 0.1 cm. square. Since there was no possibility of a shunt, the reduced systemic oxygen saturation must have been a reflection of the pulmonary findings, the cardiac failure, or both. The history of progressive dyspnea and terminal right-sided failure is compatible with the anatomic obstruction. It should be noted that the right ventricle was not in failure at the time of catheterization, as was evidenced by the normal diastolic pressure and the normal pressure in the right atrium. The marked hypertrophy of the right ventricle, which was suggested by physical examination, the electrocardiogram and the roentgenograms, was due to the increased resistance against which it had been working. The elevated pulmonary arterial pressure explains the loud pulmonic second sound [*6*]. The cause of the murmur is uncertain, but nonspecific systolic murmurs have been described in previous reports [*1*].

Before the patient's death it was realized that none of the clinical diagnoses which were considered afforded a satisfactory explanation for the greatly elevated pulmonary capillary pressure. In reviewing the data, it is apparent that this finding is most significant. Figure 4 shows the pulmonary capillary pressures recorded in this laboratory in thirty-five cases of congenital heart disease of various types, in fourteen cases of mitral stenosis, and in one case of constrictive pericarditis. The highest individual pulmonary capillary pressure in the congenital group was 20 mm. Hg; the average was 9 mm. Hg. Until the present case, a pulmonary capillary pressure of more than 20 mm. Hg had never been recorded in this laboratory in a child less than four years old. Other workers in the field, particularly Dexter [*9,10*], support the concept that the pulmonary capillary pressure is not elevated in the congenital cardiac abnormalities commonly encountered. It is also accepted generally that the pulmonary capillary pressure is not elevated in patients with chronic pulmonary disease [*9,11*].

If the pulmonary capillary pressure is accepted as a reflection of the pressure beyond the pulmonary arterioles [*2,3*], an elevation of this pressure, in the absence of left ventricular failure [*9*] or constrictive pericarditis [*12*], would suggest that there is some obstruction to the flow of blood from the lungs to the left ventricle. The most common cause of such an obstruction is mitral stenosis; however, the abnormal septum in cor triatriatum can have the same effect. It

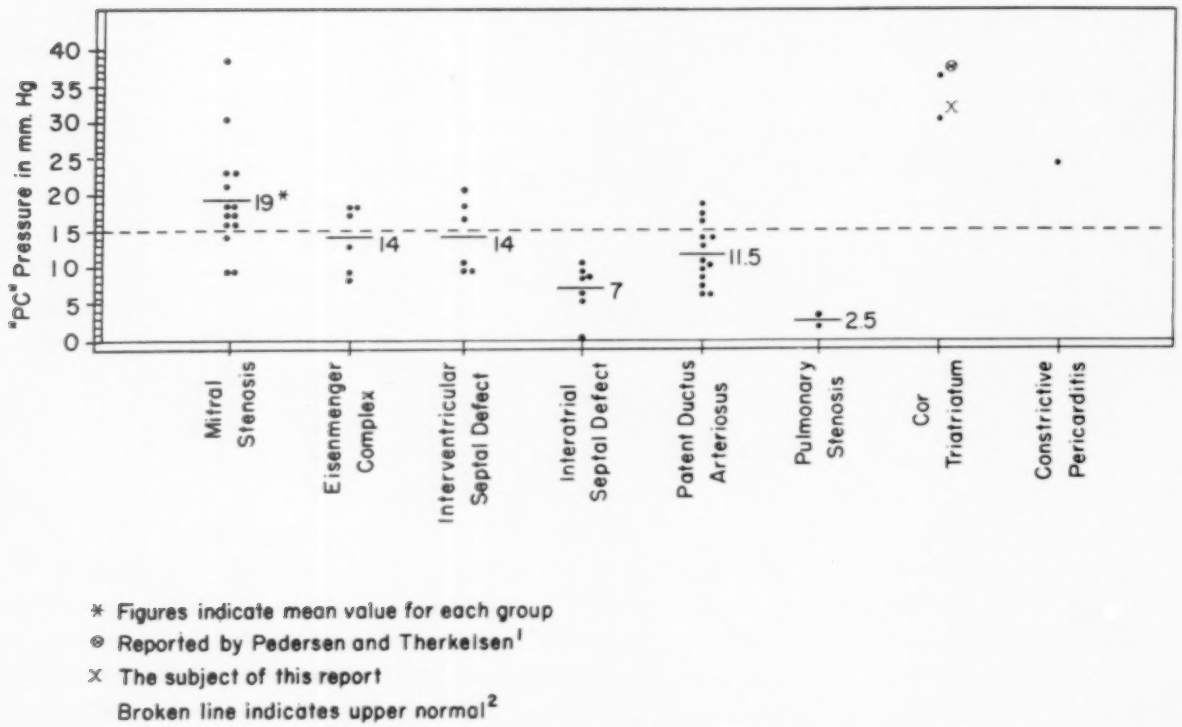


FIG. 4. Pulmonary capillary pressures in various heart conditions.

should be noted that in six of the twenty-two cases of cor triatriatum previously reported, a communication between the anomalous chamber and the right atrium was present [*1*]. Such a combination of defects would probably produce no significant elevation of the pulmonary capillary pressure. Physiologically this would resemble mitral stenosis associated with an interatrial septal defect (Lutembacher's syndrome) [*13,14*].

That cor triatriatum and mitral stenosis are functionally almost identical is supported by the findings reported here and by those of Pedersen and Therkelsen [*1*]. The clinical picture of each of these conditions is one of pulmonary congestion and right-sided heart failure. The pulmonary vascular changes are similar [*8*], and the physical findings and accessory clinical data may also be very similar. In both of these disorders there is an obstruction of flow from the lungs to the left ventricle, and in both there is an elevation of the pulmonary capillary pressure. Even the P waves of the electrocardiogram in the present case are not unlike those which may be found with mitral stenosis. The age of the patient is not an absolute differentiating point, for even though acquired mitral stenosis would be most unlikely in a small child, the possibility of congenital mitral stenosis, although rare, must be considered [*7*]. The diagnosis may depend on surgical exploration.

If in a given instance, therefore, the differential diagnosis lies between cor triatriatum and mitral stenosis, and if the patient's condition warrants definitive diagnosis and treatment, surgery is indicated. It should be remembered that in cor triatriatum the auricle opens into the left atrium below the abnormal septum, and that when the usual auricular approach to the mitral valve is used, the defect may be overlooked unless the entire atrium is explored. There is every reason to believe that surgical removal of the abnormal septum in cor triatriatum would give a gratifying physiologic result. Such a procedure would offer benefits similar to those of commissurotomy in mitral stenosis without the danger of producing mitral regurgitation.

SUMMARY AND CONCLUSIONS

1. A case of cor triatriatum is reported. In spite of extensive studies, including cardiac catheterization, the diagnosis was not made antemortem. It is not difficult, however, to correlate the clinical picture and catheterization data with the postmortem findings.

2. At postmortem examination, an anomalous septum with a small opening was found to divide the left atrium into two chambers, one communicating with the pulmonary veins and one with the left ventricle. Thus, as in mitral stenosis, there was an obstruction to the flow of blood from the lungs to the left ventricle.

3. The similarity of cor triatriatum to mitral stenosis, both clinically and physiologically, is discussed. When the pulmonary capillary pressure is markedly elevated, and when right ventricular hypertrophy and pulmonary congestion are prominent features, cor triatriatum should be considered in the differential diagnosis, particularly in the younger age groups and in atypical cases.

4. Now that surgical correction of this rare congenital anomaly is feasible, every effort should be made to establish the diagnosis.

ADDENDUM

Since this article was submitted for publication, six additional cases of cor triatriatum have come to our attention [*15–20*]. It is of interest that the case reported by Lewis and associates is the only reported case in which the diagnosis of cor triatriatum was made antemortum and therapy instituted. The authors would like also to report two additional patients who have since been diagnosed at this institution.

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Comparison of Serum Phosphohexose Isomerase Activity and Urinary Calcium Excretion in a Patient with Metastatic Mammary Carcinoma*

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During the past few years several objective criteria have been proposed for the evaluation of responses to palliative treatment in patients with metastatic cancer [*1–7*]. Among such proposed criteria are the changes in urinary calcium excretion in patients with cancer of the breast who have hypercalciuria secondary to osteolytic metastases [*3,4*] and alterations in serum phosphohexose isomerase activity in patients with metastatic cancer of the breast or the prostate [*5,6*]. It is the purpose of this paper to present a nine months' study of a patient with carcinoma of the breast and osseous metastases in which these two parameters were compared to each other and to the clinical course of the patient.

MATERIALS AND METHODS

The patient, whose history will be reported in detail, was hospitalized on the metabolic ward during the latter half of the study. Dietary calcium was restricted to 200 mg. per day or less during hospitalization. The following chemical methods were used: Urinary calcium, Fiske and Logan [*8*]; serum calcium, Clark and Collip [*9*]; serum phosphohexoisomerase, Bodansky [*10*]; serum alkaline phosphatase, Bodansky [*11*]. The normal values for these determinations are as follows: urinary calcium, 50 to 150 mg. per twenty-four hours (on a 200 mg. intake); serum calcium, 9.2 to 10.8 mg. per 100 cc.; serum isomerase, up to 40 units; serum alkaline phosphatase, 1.5 to 4.0 units. Blood counts and hematocrits were determined frequently because of myelophthisic anemia which was a prominent complication. Roentgenograms of the skeleton were taken at approximately six- to eight-week intervals. The clinical, roentgenologic and laboratory data were correlated and are outlined in Figure 1.

CASE REPORT

A thirty-four year old woman first noted a small lump in her right breast in July, 1951. She sought no treatment until December, 1951, when she underwent a right radical mastectomy. The pathologic report was infiltrating duct carcinoma with negative lymph nodes. She made an uneventful recovery and did not receive postoperative radiation. In July, 1953, intermittent pain developed in her hip and in the fall of that year she experienced fatiguability, weakness and recurrent nausea and vomiting. In addition to these symptoms she had petechiae, increasing pallor and bruised easily. She was admitted to the hospital with these symptoms in October, 1953.

At the time of admission she appeared pale and chronically ill. Examination revealed scattered ecchymotic areas over the limbs and thorax and petechiae on both legs. The radical mastectomy scar was well healed with no evidence of recurrent tumor in the scar. The spleen and liver were both enlarged. Laboratory findings revealed marked myelophthisic anemia, and a skeletal survey showed extensive osseous metastases. There was no evidence of pulmonary spread. Clusters of tumor cells were seen in the marrow.

She was treated initially with cortisone to control the hemorrhagic manifestations. Subsequently she received a total of 1,750 mg. of testosterone propionate intramuscularly over a thirty-six-day period but this treatment had to be terminated because of the development of hypercalcemia. The patient experienced subjective improvement after recovery from the hypercalcemia, but there was no improvement in the myelophthisic anemia. Consequently castration by

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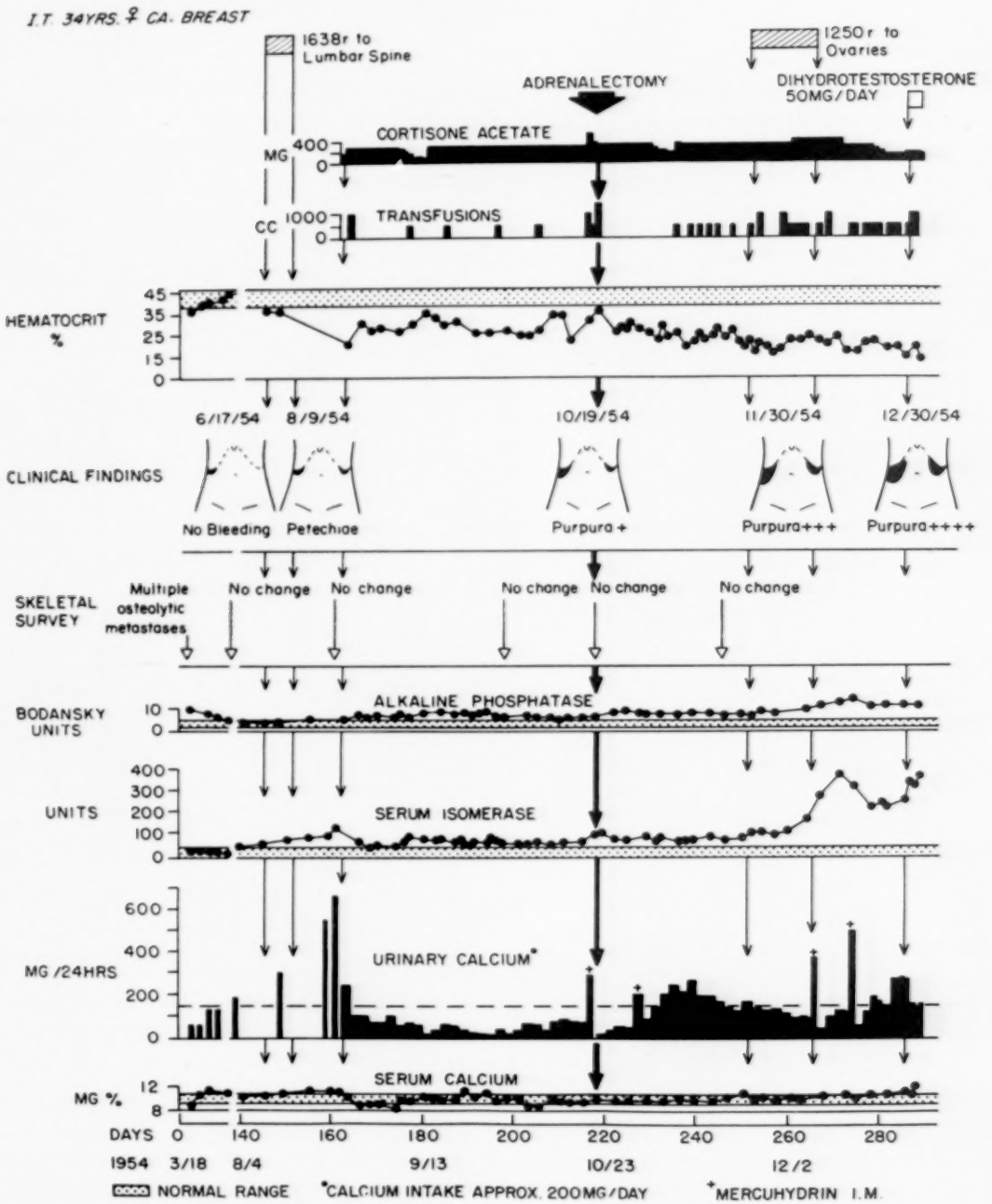


FIG. 1. Clinical and biochemical data on a thirty-four year old woman who had carcinoma of the breast with hepatic, splenic and widespread osseous metastases.

radiation was carried out, a total of 1,921 r having been delivered to each ovary. Following this treatment there was a striking remission of the disease as manifested by a complete disappearance of the myelophthisic anemia with regression of the hepatosplenomegaly and healing of some osteolytic lesions. The patient was well enough to return to her full time duties as a housewife and mother of three children. She was discharged from the hospital at the beginning of her clinical improvement on February 13, 1954, and was followed-up in the outpatient department. The details of this aspect of her course have been recently reported [*12*].

The present study, period 1, covered the time from March 18 to August 20, 1954. The first phase of the study began at the height of the patient's clinical remission when she was attending the outpatient clinic. Figure 1 illustrates the various parameters and the clinical condition of the patient from this time until December 31, 1954, the day of her death.

During the five months of observation in the outpatient clinic, the twenty-four hour urinary calcium excretion was determined on five separate occasions. As may be seen in Figure 1, the first four values were normal. At these same times the serum isomerase activity was also normal, varying from 9 to 25 units. The serum alkaline phosphatase gradually decreased, however, to a normal level of 3.8 units on July 22. These findings were associated with clinical evidences of a continued castration remission. A skeletal survey on July 22 showed no increase in the extent of osseous metastases as compared with previous x-rays. In the early part of August, following a hayride, pain developed in the patient's lower lumbar spine. Her twenty-four-hour urinary calcium excretion on August 2 was 193 mg., which is slightly above the upper limit of normal. The serum isomerase at this time was also slightly elevated to 47 units. There was no enlargement of the liver or spleen although a suspected Riedel's lobe was palpable. The patient's myelophthisic anemia remained in remission as evidenced by normal values for the hematocrit and platelet count and by the absence of bleeding.

She was admitted for one week on August 8 for radiation therapy to her lumbar spine and received a tissue dose of 1,638 r over a five-day period. Slight splenic enlargement was noted on examination. The serum isomerase activity on August 9 was definitely elevated (61 units) and the twenty-four-hour urinary calcium excretion determined on August 12 was elevated to a level of 300 mg. The hematocrit had decreased slightly to 35 per cent on August 12. Despite these laboratory findings she did not present the clinical picture of generalized reactivation of her disease.

Period 2 covered the time from August 21 to October 19, 1954. After discharge on August 15, the patient's condition rapidly became worse and she had to be readmitted on August 21. During the brief interval between admissions she had lost weight and had had increased bone pain and persistent vomiting. On examination petechiae and a palpable spleen were noted. The urinary calcium had risen to 657 mg. on August 24 and the serum isomerase activity increased to 94 units on August 23 and 128 units on August 25. The levels of serum alkaline phosphatase were normal. The platelet count dropped progressively to a value of 23,000 per cu. mm. on August 25 and the hematocrit had declined to 20 per cent by August 26. Because of this rapid recurrence of her myelophthisic anemia, a regimen of cortisone acetate, 300 mg. daily administered intramuscularly was started on August 26. The evidences of myelophthisis persisted, however, and included petechiae, a retinal hemorrhage, thrombopenia and nucleated red cells in the peripheral blood. Slight splenic enlargement, which was noted in August, had not increased by mid-October. The hematocrit was maintained between 25 to 33 per cent by repeated blood transfusions. (Fig. 1.)

The urinary calcium excretion decreased to normal levels within two days after cortisone was started and remained below 100 mg. per day for approximately eight weeks. However, except for a transient decrease to the upper limit of normal on September 1 and 2, the serum isomerase remained elevated at levels ranging up to 87 units for this same eight-week period. Slight increases in serum alkaline phosphatase activity were associated with minor rises in bromsulphalein retention. Although the administration of pharmacologic doses of cortisone failed to result in any improvement, it may be noted that a decrease in the dosage for a six-day period (September 7 to 12) was associated with a moderate worsening of her symptoms.

Since the patient had previously responded to radiation castration and therefore presumably had an estrogen-sensitive tumor, removal of the adrenals as the last remaining source of estrogen was thought advisable [*13*]. Adrenalectomy was accordingly performed on October 20, 1954.

Period 3 covered the time from October 20 to December 31, 1954. The operation was carried out without undue bleeding despite marked thrombocytopenia, and the patient withstood the procedure well. From November 2 to November 6, the dose of cortisone was progressively reduced to 150 mg. per day in an attempt to evaluate the adrenalectomy independent of the effects of pharmacologic doses of cortisone. This reduction was associated with a rise in urinary calcium excretion from 75 mg. on October 30 to 230 mg. on November 6. On this latter day the patient had increased petechiae, epistaxis and an increased degree of thrombocytopenia. Accordingly the cortisone dosage was raised to 350 mg. on November 7 and then continued at the former level of 300 mg. per day. The urinary calcium excretion remained at somewhat elevated levels for several days, but then returned to normal levels. In spite of the somewhat greater excretion of calcium during the postoperative period, a skeletal survey on November 17 showed no evidence of increased osteolytic disease. The decline in the hematocrit was more pronounced during the postoperative period and beginning November 6 more frequent transfusions were required to maintain the level at about 25 per cent. The serum isomerase activity which had risen to 103 units on October 22, averaged about 75 units until November 22. The levels, in general, were somewhat higher than those in the several weeks preceding operation.

Despite some increase in well-being, the continued anemia, thrombocytopenia, enlarging spleen, and increased serum isomerase activities led to the conclusion that the patient had not responded to adrenalectomy. Therefore, in view of the possibility that there was some residual ovarian function, it was decided to radiate the ovaries again. A tissue dose of 1,250 r was administered to the patient from November 23 to December 7. During this period the urinary calcium

excretion remained unaffected, averaging about 100 mg. per day. The serum isomerase, however, rose steadily, reaching a value of 158 units on December 6.

No clinical benefits were observed as a result of this ovarian radiation nor from a four-day course of dihydrotestosterone (50 mg. intramuscularly per day) given terminally in a final attempt to halt the progression of her neoplastic disease. The last month of her life was marked by an increasing number of complications. The purpura became more widespread, and profuse epistaxis occurred on one occasion. In addition, signs of cardiac failure developed and a pericardial friction rub was heard on two occasions. The dose of cortisone had to be varied on the one hand in an effort to control the hemorrhagic manifestations and on the other hand to avoid itensifying the signs of cardiac failure. Mercurials were administered on three different occasions during period 3 to control peripheral edema, and on each occasion distinct rises in urinary calcium were observed varying from 200 to 480 mg. per twenty-four hours. The patient also had increased enlargement of the liver and spleen and although serum determinations performed on December 13 revealed evidence of impaired liver function (serum bilirubin, 3.8 mg./100 cc.; bromsulphalein,® 19 per cent retention; total protein, 5.3 gm./100 cc.) there was no definite evidence of metastatic disease in the liver. In fact no soft tissue metastases could be demonstrated clinically and no pulmonary metastases were present on repeated roentgenograms of the chest.

The serum isomerase rose to 364 units on December 13 and remained in this range until the patient's death on December 31. The urinary calcium rose preterminally to about 250 mg. per day for several days. The hematocrit decreased steadily to a final value of 13 per cent and despite an increased number of replacement blood transfusions the patient died.

Postmortem examination revealed externally diffuse petechiae and slight icterus. There was no evidence of recurrent tumor in the left radical mastectomy scar. The liver weighed 2,500 gm. and although only approximately 10 per cent of the liver parenchyma was grossly involved by tumor nodules, diffuse hepatic permeation by tumor was noted microscopically. The spleen weighed 1,150 gm., approximately six times the normal size, and was almost totally replaced by tumor tissue. Tumor also replaced the esophageal and periaortic nodes and infiltrated the bone marrow uniformly. No metastases were noted in the lungs. The ovaries were fibrotic and showed extensive invasion by tumor. The adrenal glands were surgically absent and no accessory adrenal tissue was noted. The other findings related primarily to the hemorrhagic complications. Dark blood was present in the gastrointestinal tract, and superficial ulceration of the rectal wall secondary to intramural hemorrhage was noted. The lungs showed small foci of resolving hemorrhage. The pericardial cavity contained about 70 cc. of dark bloody fluid and an extensive intramural hemorrhage of the entire right auricular appendage was seen. There were hemorrhages in both renal pelves; left pyelonephritis and bilateral acute membranous glomerulonephritis were noted on microscopic examination.

COMMENTS

Much of the usefulness of objective measurements which indicate tumor activity lies in their ability to aid in the early detection of exacerbation of neoplastic disease. It has been pointed out that a rising urinary calcium excretion is a good index of developing osteolysis [*4,12,13*] and hence is of help in the early detection of tumor progression. In period 1 it is of interest, therefore, that the first signs of progression of disease were the slight rises in serum isomerase and urinary calcium noted on August 2. It should be noted, however, that these signs did not precede the appearance of lumbar back pain although the possibility exists that more frequent determinations of these parameters might have revealed signs of relapse prior to the appearance of pain. The fact that the skeletal survey of July 22 did not show evidence of new lesions is not surprising since tumor growth which proceeds at a slow rate may not reveal itself by roentgenographic changes for many weeks. However, by the first part of August the rate of growth of tumor had increased to a point where the calcium excretion was slightly abnormal (193 mg. per twenty-four hours). The isomerase level was also slightly elevated as noted, and although neither elevation was very striking, the simultaneous increases compared to previously normal values indicated that the patient's disease was in early but generalized relapse. This was not fully appreciated at the time because of her good clinical status and the absence of recurrent anemia. Hence she was initially treated only with local radiation to the painful area in her lumbar spine. More vigorous systemic measures might well have been undertaken at this point.

The slight but definite decrease in the serum alkaline phosphatase to normal levels in period 1 might be interpreted as biochemical evidence of relapsing disease. Decreases in serum alkaline phosphatase have been described [*14*] as heralding the onset of hypercalcemia in carcinoma of the breast which in turn may indicate exacerbation of disease.

What was biochemically apparent in the early part of August became clinically evident later that month. Definite clinical signs of progression were associated with marked rises in the urinary

calcium and serum isomerase activity, and the rapidity with which the myelophthisic anemia recurred was remarkable. Up to this point there had been good parallelism between the urinary calcium excretion and serum isomerase activity. Because of the rapid development of thrombopenia and bleeding, cortisone was administered. The urinary calcium rapidly returned to normal and remained there for approximately two months, the interpretation of these data being that the rate of growth of tumor in the bones had been slowed as a result of this treatment with consequent disappearance of hypercalciuria. Yet, aside from a transient drop to normal levels, the serum isomerase remained above normal despite treatment and provided evidence of continued tumor activity. As has been noted previously [*5*] such dissociations between the isomerase activity and the urinary calcium have usually been associated with growth of tumor in tissues other than bone. It was assumed in this case that tumor was present in the liver or other soft tissue although unequivocal evidence of this did not become apparent until autopsy.

In view of the patient's previously good response to castration, adrenalectomy was next performed. It is interesting that this procedure was successfully carried out despite a platelet count of 20,000 per cu. mm. with associated generalized petechiae and purpura. Following operation the isomerase levels tended to be somewhat higher than they were preoperatively, and more blood transfusions were needed to sustain the hematocrit. These observations suggested a persistence of tumor activity. The falling hematocrit was a reflection of more severe myelophthisis plus a shortened red cell survival time (determined in another study [*15*]). Although a rising urinary calcium as an associated feature of increasing myelophthisis may be seen because of increased skeletal breakdown by tumor, the urinary calcium in this patient remained within the normal range except for a few days when it rose to a range of 200 mg. per day. A possible explanation of this is that the tumor spread through the marrow cavity destroying less bone but causing more anemia than if it had spread through cortical bone. Despite being in the normal range for the most part, the urinary calcium excretion was consistently higher during this period as compared to preadrenalectomy values. Again there was no roentgenographic evidence of progression of disease, but the data were interpreted as indicative of some bone destruction relative to the preadrenalectomy period.

It must be admitted that the urinary calcium derives from a net balance between bone formation and resorption. In patients with osseous metastases this process may be complicated by simultaneous osteolytic and osteoblastic areas in the same skeleton. Hence an equally valid interpretation of the urinary calcium data in the postadrenalectomy period would be that there was simply diminished osteoblastic activity without any change in the rate of bone breakdown. Likewise it is conceivable that the proportions of fecal and urinary calcium may alter without any change in the net balance. We have no fecal calcium data on this patient and hence can do no more than speculate. Lastly general metabolic factors, some of which have been quantitatively defined [*16,17*], may affect calcium excretion but these were controlled as completely as possible. There was no disturbance of acid-base balance throughout the study. The transient rises in urinary calcium incident to administration of mercurials were regarded as secondary to water diuresis although an independent effect on the tubular reabsorption of calcium excretion cannot be excluded.

Clinical and laboratory evidence indicated that the patient had failed to respond to adrenalectomy, and in the remote hope of achieving a second castration response, her ovaries were re-radiated. Again, improvement failed to occur and the patient followed a gradual downhill course that was paralleled by rising serum isomerase activities and falling hematocrit levels. Abnormal liver function noted at this time tended to support the idea that the isomerase levels were reflecting active soft tissue disease in the liver although there was no biopsy proof of liver metastases. In the last weeks of her life she presented a clinical picture which was suggestive of a lymphomatous disease or leukemia, with purpura, anemia, thrombopenia and hepatosplenomegaly. Although a coincidental leukemia may conceivably develop, at no time did the peripheral blood picture or bone marrow suggest such a diagnosis. Her death was primarily attributed to cardiac failure and hemorrhagic pericarditis (without evidence of effusion or tamponade). In this terminal period there was no acute elevation of blood pressure or rise in the blood urea nitrogen and the urinary sediment contained no red blood cells or casts. Hence, the finding of acute membranous glomerulonephritis

at postmortem examination was a pathologic entity without attendant clinical signs or symptoms.

The gross postmortem findings gave a transient impression of a lymphomatous disease with massive involvement of the spleen, lymph nodes and marrow. The various hemorrhagic manifestations completed the similarity to a lymphoma. However, microscopically these organ systems and the liver as well were diffusely and almost completely infiltrated by carcinoma. It was obvious that the involvement of these tissues accounted for the high serum isomerase activity, there being no other significant areas of soft tissue disease. From the gross and microscopic examination of the bones it was apparent that the tumor invaded the marrow cavity almost exclusively. Pathologic fractures and complete bone destruction were not noted and hence the earlier speculation of marrow permeation versus cortical bone destruction as an explanation for the dissociations between urinary calcium and hematological findings is supported by the pathologic data.

SUMMARY

A study of a patient with metastatic cancer of the breast is presented in which two parameters of tumor activity, serum isomerase and urinary calcium, were determined over a nine-month period. The usefulness, limitations and interpretations of these parameters are discussed in the light of the patient's clinical course.

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Chronic Systemic Melioidosis

*Review of Literature and Report of a Case, with a Note on Visual Disturbance Due to Chloramphenicol**

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MELIOIDOSIS is a disease of man caused by the bacterium Malleomyces pseudomallei, which is related to the causative organism of glanders. It is primarily a disease of rodents, cats and dogs of a rather limited Oriental area, but it is not widespread among these animals. Over 300 cases in man have been reported [*1*]. Melioidosis is endemic to Indochina, Ceylon and the Dutch East Indies. Two cases have been reported in American armed services personnel on Guam [*2*] and one case on the Philippine Islands [*3*]. Only two cases have been reported in persons who have never left the United States [*1,4*]. However, a case has been reported in a man who had left the United States to reside in the Panama Canal Zone for only two years [*5*]. These three cases are the only known instances of melioidosis from the Western Hemisphere.

Melioidosis (Whitmore's disease) was first described in 1912 by Whitmore [*6*], a pathologist at a hospital in Rangoon. He demonstrated the disease at postmortem examination in the "ill-nourished, neglected wastrels of the town," describing it as a "glanders-like disease" but differentiating it from glanders [*7*]. In 1913 Whitmore reported thirty-eight fatal cases of melioidosis, 31 in morphine addicts [*7*]. Most of his postmortem examinations were of natives found dead on the streets. All had had the acute form of the disease.

The disease was first diagnosed antemortem by Stanton in Malaya in 1917 [*8*]. He subsequently found fourteen cases among 3,069 autopsies in Malaya [*9*].

The acute form of Whitmore's disease is the type most often recognized in man, constituting all but twenty-three of the reported cases. The rather sudden onset is characterized by moderately high fever, signs of acute pulmonary infection and occasionally diarrhea. This is followed rapidly by signs of miliary visceral abscesses, prostration and death in a few days. All of Whitmore's cases and all but two of Stanton's cases were of this type. The reports of Cox [*10*] and Mirick [*2*] (American armed forces personnel in Burma and Guam, respectively), also are of patients with the acute form of the disease.

The chronic form of melioidosis usually develops in patients who survive the acute disease. Some cases have been reported in patients who first manifested the disease after leaving an endemic area. The clinical characteristics of chronic melioidosis may be similar to those of a disseminated fungus infection or tuberculosis. Small, discrete and confluent abscesses appear subcutaneously and in the viscera and bones. Draining sinuses are common. Spontaneous, temporary remissions occur but the sluggish abscesses persist in many organs, the patient dying in months or years. There are seventeen reported cases of chronic disseminated infection.

Green [*11*] has placed in a special category those chronic cases, without fever, manifested by subcutaneous adenitis or superficial ulcers in which recovery follows formation of a sinus or treatment with drugs. He called them "afebrile cases." He reports one case and quotes four other similar cases. Peck [*12*] observed a patient similar to those reported by Green. The value of such a classification is doubtful since several cases of disseminated infection have followed otherwise asymptomatic cutaneous abscesses and adenitis [*4,5,8*], and the follow-up period in some of the reported "afebrile cases" is not long. We could find only six cases that would fit this category.

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Organism. M. pseudomallei, also known as Pfeifferella whitmori or Whitmore's bacillus, is a gram-negative, bipolar staining, pleomorphic bacterium. It is readily isolated on ordinary media. It differs from Malleomyces mallei, the causative organism of glanders, in being motile and attacking a wider range of carbohydrates. It is virulent for guinea pigs, rats, rabbits, mice, hamsters and monkeys.

The Straus reaction is diagnostically significant. A few days after the intraperitoneal injection of infective material, acute orchitis secondary to peritonitis develops in male guinea pigs. The testes are displaced into the scrotum. Culture from the pus of the testes or other organs of the animal can then be made to isolate the organism.

Nigg et al. [*13*] noted that mice frequently died soon after inoculation with viable organisms but showed no gross lesions at autopsy. This phenomenon prompted them to investigate the toxicity of bacteria-free filtrates of broth cultures. Their work strongly suggests that M. pseudomallei produces an endotoxin which increases quantitatively as autolysis proceeds in culture. Slight immunity against infection appeared to be produced in animals by toxic filtrates which were detoxified by heat.

Cravitz [*14*] has shown the complement fixation tests to be specific for infection with members of the Malleomyces group but has not been able to use it to differentiate between glanders and melioidosis. Both organisms appear to have a common non-protein antigen. He found the agglutination test to be more sensitive than the complement fixation test, but practically all normal serums gave agglutination in low titers. A rising titer in the agglutination test has greater diagnostic value than a single titer. Case v of Harries [*15*] demonstrates the value of the agglutination test when cultures are negative early in the disease.

Transmission. Human beings are not readily infected with M. pseudomallei, the disease being rare even in endemic areas where conditions favor its dissemination. Man-to-man transmission has never been reported.

In the East, natural infection has been reported in rats, rabbits, domestic cats and dogs. Pigs in Madagascar [*16*] have been reported to be healthy carriers of the bacillus. In contrast to the causative organism of glanders, equines and cattle are usually immune. Only one horse has been found to be naturally infected, as evidenced by a nasal discharge. One instance has been recorded of a cow [*17*] with a splenic abscess. All attempts by Stanton [*18*] to infect horses were unsuccessful.

Most of the cases described by Whitmore were in addicts who took morphine by injection. It was assumed that the disease was transmitted by this means. Indeed, Knapp [*19*] referred to melioidosis as "morphine injector's septicemia."

Stanton [*20*] noted a choleraic onset of the disease in several human beings. An epizootic occurred in his laboratory animals, apparently due to food contaminated by wild rats, and he was impressed by the ease with which animals were infected by the oral route. These observations suggested to him that infection in man is subsequent to contamination of food by rat excreta, the intestinal tract being the portal of entry.

Stanton's postulate of an intestinal mode of infection has remained the most popular explanation of human infection but it is still unproved [*21*]. The common occurrence of cutaneous and respiratory lesions as an initial clinical manifestation of melioidosis suggests other portals of entry.

Rats are thought to be the primary reservoir [*21*] but conclusive evidence is lacking. Even in the immediate vicinity of human cases the organism frequently cannot be isolated from rats. Harries [*15*] examined 500 rats near Rangoon but found no instance of infection to account for his five cases in man. Experimentally the disease can be transmitted by the rat flea Xenopsylla cheopsis [*22*] and by the mosquito Aëdes aegypti [*23*].

Pathology. The essential lesions in melioidosis are disseminated, sharply defined, minute abscesses with granulomatous margins filled with caseous pus. They begin as a collection of neutrophils surrounded by a zone of congestion [*20*]. The small areas of necrosis coalesce with their neighbors to form a honeycombed lesion. In the liver the pus is "glairy greenish" in color [*24*]. Giant cells are present but epithelioid cells are few in number.

Abscesses may occur in any organ, but they are more common in the lungs, liver, spleen, kidneys, lymph nodes and bones. We could find no report of a brain abscess.

CASE REPORT

A vesicular eruption developed on the hands and feet of W. G. (No. 6609) a thirty-two year old white

American soldier during the last two and a half months of his year's stay in the Philippine Islands. After his transfer to Okinawa the rash became more severe over a period of two months. He was admitted to a hospital in the Philippines on October 19, 1945. There was edema, exudation and vesiculation of both hands, some interphalangeal fissuring and moderate involvement of the toes. The vesicles varied in size but were not over approximately 3 mm. in diameter. Leukocytes were 6,680 per cu. mm. with 63 per cent neutrophils, 29 per cent lymphocytes, 3 per cent monocytes and 4 per cent eosinophils. Treatment consisted of boric acid compresses and Burow's solution, but the rash failed to heal.

On December 13, 1945, the patient was admitted to Oliver General Hospital in Augusta, Georgia, as a transfer from overseas. Physical examination was normal except for the vesicular eruptions of the hands and feet. Leukocytes were 13,450 per cu. mm. with 70 per cent neutrophils, 1 per cent monocytes, 1 per cent basophils and 28 per cent lymphocytes. Hemoglobin was 90 per cent of normal; blood sedimentation rate, 11 mm./hour; the serologic test for syphilis was negative; and x-ray of the chest was normal. No cultures were made of the skin lesions, and biopsy was not performed.

One day after admission to the hospital a urethral discharge developed which persisted in spite of penicillin therapy. The discharge contained many pus cells but no organisms were identified on repeated stains and cultures. When urticaria developed penicillin was discontinued. The urethral discharge was then effectively controlled by the administration of typhoid vaccine. The skin rash for which he was originally admitted gradually subsided, and he was discharged with a diagnosis of pompholyx of the fingers and hyperhidrosis of the hands and feet.

The patient was discharged from the army on March 4, 1946, and returned to his former occupation as a welder of galvanized pipe on ships in New Orleans. In the winter of 1947 he had a severe cough with fever and pain in the left side of the chest. Symptoms persisted for one month. Frequent upper respiratory infections and a cough productive of a moderate amount of yellow, foul-smelling sputum followed.

On May 12, 1948, he was examined at a private clinic. The temperature was 99.2°F. Physical examination was normal. X-ray of the chest revealed irregular areas of consolidation in the mid-portion of the left lung field. There was a leukocytosis of 12,800 per cu. mm. with 75 per cent neutrophils. He was followed-up as an out-patient. After x-rays showed enlargement of the shadows in the left lung field, penicillin was administered. This resulted in urticaria, for which he was admitted to the Veterans Administration Hospital in New Orleans on August 10, 1948.

His average weight was 156 pounds; his present weight was 145 pounds. Blood pressure was 100/50 mm. Hg; pulse, 160 per minute; and temperature, 99°F. Pertinent physical findings were limited to giant circinate urticaria of the entire body. Leukocytes were 18,050 per cu. mm. with 72 per cent neutrophils and 6 per cent eosinophils; blood sedimentation rate, 26 mm./hour (Wintrobe); and hematocrit, 45 per cent. Urinalysis was normal and has always been so. The sputum was negative for tubercle bacilli and fungi on culture and guinea pig inoculation, but Staphylococcus aureus and beta hemolytic streptococci were present. An intradermal test with the second strength purified protein derivative of the tubercle bacillus was positive; histoplasmin, blastomycin and coccidioidin intradermal tests were negative. X-rays of the chest disclosed opacities of the apex of the left lower lobe with lucencies which were shown by planigrams to be cavities.

The urticaria subsided but the patient coughed up several ounces of sputum daily and had occasional episodes of hemoptysis. A temperature in the afternoon as high as 100°F. and leukocytosis of about 14,000 per cu. mm. persisted. During forty days of therapy with sulfadiazine and streptomycin he became asymptomatic, but leukocytosis persisted and films of the chest were unchanged.

On February 2, 1949, a left lower lobectomy was performed. Multiple small abscesses were present in the lobe, from which S. aureus was grown in almost pure culture. Microscopically there were areas of central necrosis 2 mm. to 3 mm. in size containing neutrophils but only occasional lymphocytes. The central necrotic area was surrounded by a zone of collagenous tissue infiltrated by fibroblasts, lymphocytes, plasma cells and macrophages, containing varied quantities of brown, granular pigment. There were occasional areas in which multinucleated giant cells and epithelioid cells were present [*25*]. The diagnosis of the Armed Forces Institute of Pathology was "granulomatous pneumonitis, etiology undetermined."

Postoperatively the patient had a stormy course with a pneumonic process of the left upper lobe and left pleural effusion which required repeated thoracenteses despite antibiotic therapy. The pneumonia and pleural effusion subsided in several weeks.

He gradually became afebrile, felt well and gained 4 pounds. In June, 1949, he had slight fever and a cough which produced a small amount of thin white sputum. The temperature was 100.4°F., weight 134 pounds. A few rales were heard posteriorly in the left side of the chest. Leukocytes were 14,400 per cu. mm. with 55 per cent neutrophils; blood sedimentation rate, 34 mm./hour; and blood cultures were sterile. Sputum cultures yielded hemolytic S. aureus. An x-ray film of the chest was interpreted as pneumonitis of the left paracardiac region with probable abscess formation.

After treatment with penicillin, streptomycin and sulfadiazine he became afebrile. When urticaria

developed again, penicillin was discontinued. Subsequently he had a maximal daily temperature of 100°F., coughed up approximately 200 cc. of sputum per day and complained of a dull pain in the left side of the chest which was unrelated to respiration. He became afebrile after therapy with penicillin "O," but the supply of this drug was quickly exhausted. Only a partial febrile response was noted from therapy with chlortetracycline (aureomycin®) and chloramphenicol (chloromycetin®).

On August 15, 1949, a left upper lobectomy and a partial left thoracoplasty were performed. The lobe contained firm nodules 0.5 cm. to 2.0 cm. in diameter. The microscopic picture was similar to that in the previously resected lobe, and "granulomatous pneumonitis, etiology undetermined" was again the diagnosis of the Armed Forces Institute of Pathology. Postoperatively he had slight hemoptysis for a few months and a bloody pleural effusion which required repeated thoracenteses. Subsequently an empyema developed on the left side from which organisms were not cultured. Chloramphenicol, streptomycin and sulfadiazine were administered. He improved slowly, and on December 16, 1949, the left thoracoplasty was completed with resection of the first, second and seventh ribs. After thoracoplasty, open drainage was instituted. He improved gradually over several months' time. The wound healed, sputum production decreased, and he gained weight. An x-ray of the chest taken on June 7, 1950, disclosed no fluid in the left side of the chest, and the right lung was normal.

In September, 1950, the patient had a sudden, dull ache in the left inguinal and femoral regions, with tenderness and spasm of the adductor longus muscle. X-ray films of the left hip and pelvis were normal, and the chest showed no change. Leukocytes were 13,050 per cu. mm. with 68 per cent neutrophils. After physiotherapy the pain subsided. From December, 1951, to December, 1952, there were numerous admissions for pain in the left side of the chest, low grade fever, occasional hemoptysis and finally a recurrence of the left sided empyema. Over a period of several weeks an infiltration appeared in the right lung but this subsided during chloramphenicol therapy, which he received for the greater part of the year. The empyema space was effectively drained, and the left eight and ninth ribs were resected. In January, 1953, his general condition became progressively worse. A mass in the right upper quadrant with symptoms and signs of acute peritonitis appeared.

On January 20, 1953, an exploratory laparotomy was performed. Multiple small abscesses of the liver were encountered, and free pus was present in the peritoneal cavity. Cultures and biopsy of the liver abscess were performed but no etiologic diagnosis was made. The guinea pig into which the pus was inoculated died in several days, and cultures from the viscera were overgrown with a strain of Proteus. The histologic picture of the abscess of the liver was similar to that previously described for the lesion of the lung. However, there was a scarcity of neutrophils, and a few flecks of calcium were present in the necrotic substance [*25*].

His condition improved greatly by April, 1953, but during the next month fever and hemoptysis recurred. A roentgenogram of the chest showed increased infiltration in the right upper lobe with evidence of cavitation. After the patient had received chloramphenicol for two months, considerable resolution was apparent. By June, 1953, his temperature remained under 100°F., and chloramphenicol was discontinued.

The patient gained weight during the next four months and felt relatively well. However, in October, 1953, slight fever, increase in cough and pain in both sides of the chest occurred. His weight was 116 pounds; temperature, 99°F. Wheezes were heard in the chest. The hematocrit was 44 per cent; blood sedimentation rate, 40 mm./hour; leukocytes, 8,600 per cu. mm. with 72 per cent neutrophils. The serum albumin was 4.8 gm./100 ml.; globulin, 3.1 gm./100 ml.; zinc turbidity, 5.1 units; blood culture, negative. Blood chemical tests of hepatic function were normal. A sputum stain showed many gram-negative rods and a few gram-positive cocci. A culture was reported as Pseudomonas aeruginosa and S. aureus. An x-ray of the chest disclosed an increase in the infiltration in the right upper lobe, and the disease had a more exudative appearance.

Fever, with a temperature usually as high as 101°F. in the afternoon, and pain in the left side of the chest persisted despite chloramphenicol therapy. On October 26, 1953, he experienced severe sciatica on the left side, which persisted for two months. The results of the lumbar puncture and examination of the spinal fluid were normal. Initially, roentgenograms taken of the pelvis and hip were normal. However, by November 6, 1953, destructive lesions in the left sacroiliac region and acetabulum were apparent. Concomitantly, a similar area of destruction appeared in the seventh right rib. A bone survey revealed no lesions other than these. The infiltration in the right upper lobe appeared to be a cavity with measurements of 1.5 cm. by 2.0 cm., but no fluid level was present. On December 7, 1953, in search of an etiologic diagnosis, a surgical biopsy of the seventh right rib was performed. A 6 cm. segment of destroyed rib was removed, from which Whitmore's bacillus was isolated.

In view of the results of sensitivity tests it was decided to administer chlortetracycline and chloramphenicol together with gantrisin.® Chlortetracycline was discontinued after one month because of nausea and vomiting, and tetracycline was substituted without apparent toxicity in the same dose.

By December 28, 1953, the patient was afebrile but had failed to gain any weight and had a leukocytosis of 12,400 per cu. mm. At this time there was swell-

ing of the left inguinal and femoral regions with fluctuation. Three days later the left femoral mass was opened and drained surgically of a large amount of thick, creamy pus. A sinus tract was present leading up and under the inguinal ligament. This was thought to represent a cold abscess arising from the sacroiliac joint. Cultures of the purulent material also yielded M. pseudomallei. He was completely afebrile after incision of this mass and remained so. By February 8, 1954, he gained 6 pounds but still had a slight cough. In April, 1954, both gantrisin and tetracycline were discontinued, but chloramphenicol was still administered. During this period he continued to gain weight and he felt well. Blood examination was essentially normal except for a persistent leukocytosis of about 10,000 per cu. mm.

In the latter part of 1954 and in 1955 he had three episodes of visual disturbance. One of these was due to a transient, mild iritis present in February and also in June, 1955. The other two instances of visual disturbance occurred in August, 1954, and in September, 1955. Both episodes were remarkably similar in their manifestations. There was a rather abrupt onset of visual impairment which promptly and completely improved on each occasion following cessation of chloramphenicol therapy. On both occasions no objective findings were demonstrated in the eyes. Unfortunately the visual fields were examined only after vision had improved following the first episode. Transient retrobulbar optic neuritis is probably the best explanation of these episodes.

On August 31, 1954, the patient complained of blurred vision. Objects seemed "smoky," especially those at a distance. Examination of the eyes revealed nothing to account for the visual loss. On September 7, 1955, vision in the right eye was 20/25 and in the left eye 20/30. Visual fields checked on a tangent screen were normal at this time.

In view of the eye and ear complaints of four days' duration, chloramphenicol was discontinued on September 2, 1954. During the next four days all symptoms disappeared. On December 7, 1954, chloramphenicol was administered again in doses of 1 gm. per day and gradually increased so that by December 27, 1954, he was taking 3 gm. per day. No visual difficulties re-appeared during this time. During July, 1955, he complained of slightly foggy vision again. Examination of the eyes was normal and the vision 20/20 in both eyes. There was no indication of uveitis. The symptoms continued, and by September 4, 1955, vision was so blurred that he was unable to read newsprint. Vision in the right eye was 20/400 and in the left 20/300. Visual acuity was not improved with refraction. On slit lamp examination the cornea, anterior chamber and iris were clear. The fundi were normal and the optic medium clear in both eyes. Visual fields were not tested. On September 4, 1955, chloramphenicol was discontinued and was never prescribed again. Vision improved remarkably almost immediately. Visual acuity on September 30, 1955, was 20/30 in the right eye and 20/40 in the left eye. Three days later, vision in both eyes was 20/20.

Since December 17, 1953, the patient had received chloramphenicol almost continuously, ingesting over 1,600 gm. of the antibiotic during this twenty-one month period. During the preceding four years a much larger amount of the drug had been administered.

During the first episode of optic neuritis, bilateral tinnitus appeared simultaneously with the visual complaints. Audiograms revealed no change from previous testing performed in past years as a part of the streptomycin therapy. Tests of vestibular function were normal. The high pitched "whistling" tinnitus was not ameliorated when chloramphenicol was discontinued and has persisted unchanged to the present date.

Since the visual difficulties resolved, he has been free of symptoms except for the tinnitus and slight dyspnea. Typical bronchial asthma has been present during the last few years but this is not severe.

In September, 1956, he weighed 146 pounds. Examination of his eyes and vision was normal. Despite his apparent well-being there was a leukocytosis of 12,650 per cu. mm. with 64 per cent neutrophils, and the blood sedimentation rate was 30 mm./hour (Wintrobe). Roentgenograms of the chest and pelvis disclosed no change in the past two years. The bony lesions were still present, with no evidence of healing.

Bacteriologic Studies. The bacteriologic details of the organism isolated from this patient have been reported elsewhere [*26*]. The following is a synopsis of that work.

From the resected rib and the cold abscess presenting in the femoral region was isolated a motile, bipolar staining, gram-negative bacillus which proved to be M. pseudomallei. The pus was injected into a male guinea pig, which died within twenty-four hours with evidence of peritonitis and multiple visceral abscesses histologically similar to those in the patient's lung. A bilateral Straus reaction was obtained.

Studies at the Division of Veterinary Medicine of the Walter Reed Army Medical Center were performed through the courtesy of Colonel Maurice W. Hale. These confirmed the identification of the organism. A complement-fixation test was conducted of the patient's serum, and a 4-plus reaction was obtained with 0.1 ml. of serum against M. mallei antigen. The patient's serum in a dilution of 1:320 agglutinated the organism isolated from the rib.

Tube dilution sensitivity tests showed the growth of the organism to be inhibited by the following concentration of antibiotics [*26*]:

Antibiotics	μg./ml.
Tetracycline	1.56
Oxytetracycline	3.12
Chlortetracycline	3.12
Chloramphenicol	6.25
Penicillin	25.0
Neomycin	50.0

The organism was not sensitive to large concentrations of streptomycin, bacitracin, polymyxin, erythromycin or carbomycin.

Comments. Where our patient contracted melioidosis is not clear. Of great importance is whether or not the skin lesions which appeared in 1945 while he was in the South Pacific were manifestations of Whitmore's disease. Vesicular skin eruptions have been described in chronic melioidosis [*15,27*] but they were "grape-like" and appeared in seriously ill patients. In contrast, our patient's lesions were apparently typical of pompholyx. He was afebrile and there was no leukocytosis during the height of the eruption. The leukocytosis present when he was transferred to the United States may have been related to the urethritis. It is interesting that the blood sedimentation rate was normal despite the urethritis and skin rash. The x-ray films of the chest, when appraised in retrospect, were normal at that time.

There was a two-year interval between his return to the United States, with disappearance of the skin rash, and the onset of the respiratory symptoms. This would represent a long incubation or asymptomatic period had the disease been contracted in the Pacific. The incubation period of melioidosis is unknown but has been assumed to be short [*10*]. The longest recorded period between leaving an endemic region and the appearance of clinical manifestations of melioidosis is six months, and this interval is not without dispute [*28*]. Beamer's [*4*] patient was asymptomatic for ten months after radiation of what might have been a subcutaneous lesion of melioidosis.

Only one case of Whitmore's disease has been reported from the Philippine Islands, and only three cases from the United States. The probability of our patient contracting his disease in New Orleans must indeed be small on the basis of published reports. However, it is possible that this disease is not as uncommon in the United States as the literature would suggest. The nonspecificity of the clinical picture and the close resemblance to many other common illnesses could account for many unrecognized cases.

The failure to demonstrate M. pseudomallei in the sputum or resected lung is of interest. Usually sputum cultures easily demonstrate the organism, and in several cases the diagnosis has been made by this means [*3,15*]. Our patient had received antibiotics from the beginning of his illness before cultures of the sputum were initiated. An almost pure culture of S. aureus was isolated from the lung abscess, and the sputum was not demonstrated to be pathogenic when injected into a guinea pig. This was possibly the result of inhibition of growth of Whitmore's bacillus by the streptomycin and sulfadiazine which the patient had received. In addition, every effort was made to isolate tubercle bacilli or fungi, to the neglect of ordinary sputum cultures. It is conceivable that Malleomyces was isolated from the sputum and discarded as a contaminant [*26*].

After the diagnosis was established there was no well recognized procedure to be followed in therapy. The partial response on many previous occasions to weeks and months of antibiotic therapy suggested the importance of long-term administration of the drugs, as did the presence of metastatic foci in bone.

There were several antibiotics to which the organism was sensitive. It was decided to administer high doses of three drugs concomitantly until there was healing of the bony lesions. Early in the course of therapy gastric symptoms necessitated discontinuance of the drugs for short periods of time and substitution of tetracycline for chlortetracycline. Chloramphenicol was selected for long-term administration because it caused no immediate toxic effects. It was only after prolonged therapy with this drug that what was probably neurotoxicity appeared upon two occasions.

Neurotoxic Effects of Chloramphenicol. During both of these episodes of visual disturbance nothing was found to explain the loss of vision. Unfortunately, visual field examinations were not performed at appropriate times. Nevertheless, visual acuity improved in a remarkably short period on both occasions when the administration of chloramphenicol was discontinued. Since the patient had a striking reduction in vision with no objective change in the eyes to account for it, the only reasonable explanation for the

visual loss is retrobulbar neuritis on both occasions. The temporal relationship suggested that chloramphenicol was responsible for it.

A few isolated reports suggest that chloramphenicol may conceivably affect the central nervous system. Harris [*29*] observed one patient who had severe headaches with mild signs of meningismus and another who also suffered transient visual disturbances. Mild euphoria following large single doses of the drug [*30*], as well as slight depression and confusion [*31*] have been described.

Optic neuritis following chloramphenicol therapy has been reported only twice. The first recorded instance was a patient of Wallenstein [*32*] with ulcerative colitis who received 1.5 gm. daily of the drug for nearly six months. Loss of visual acuity, bilateral scotomas and hyperemia of the optic discs with the appearance of new vessel formation on the nerve heads appeared rather suddenly. Later, there was a painful persistent peripheral neuritis of the lower extremities. Marked improvement in vision was noted immediately after administration of the antibiotic was discontinued. At the end of four months both the optic and peripheral neuritis completely subsided.

Lasky et al. [*33*] described a patient with S. aureus endocarditis who became totally blind after ingesting 6 gm. daily of chloramphenicol for six weeks. He cited this as an example of optic neuritis caused by the antibiotic. However, since the patient had recently had endocarditis and multiple retinal hemorrhages were noted at the time of visual loss it seems impossible to rule out the possibility of emboli.

It is of interest that in our patient visual abnormalities failed to recur after the first episode, when the drug was started again in small doses which were gradually increased. There was no further difficulty for eight months, when vision again diminished. This episode also responded to discontinuance of the drug. The patient reported by Wallenstein had received chloramphenicol for six months, while Lasky's patient had taken the antibiotic for only six weeks. However, Lasky's patient received six times the usual daily dose. Our patient had received chloramphenicol for twenty-one months in doses averaging 3 gm. daily and in addition had taken the drug intermittently for the previous four years. This suggests that optic neuritis due to chloramphenicol may occur following prolonged use of the drug in high doses.

The tinnitus associated with the first occasion of sudden visual changes also suggests a neurotoxic effect of choramphenicol. However, there was no objective evidence of vestibular or auditory abnormality, and the symptoms failed to improve after the drug was discontinued. Also, the tinnitus was not made worse by readministration of chloramphenicol for a prolonged period.

The chronicity of the disease in our patient is not unique. McDowell's [*5*] patient was apparently cured only after eight years of illness, and Grant [*28*] reported a man still ill at the end of five years. Nevertheless, the ten-year period in our patient is the longest illness recorded in chronic melioidosis. Perhaps the bacteriostatic effect of the antibiotics given before and after the diagnosis was made may have been a factor in the prolonged course.

The roentgenologic aspects of our case have been reported elsewhere [*34*] and will not be discussed here.

REVIEW OF CASE REPORTS OF PROVED SYSTEMIC MELIOIDOSIS

CASE I. Stanton [*9*] reported an acute, febrile respiratory illness in a young, adult Malayan. This was followed by the development of an abscess of the right foot. Multiple abscesses of the right leg continued to appear during a two-month febrile period. By the eighth month there were many osteomyelitic sinuses in the feet. The patient was treated surgically and with an autogenous vaccine. Two years later multiple sinuses were still apparent but they were culturally negative for M. pseudomallei.

CASE II. The other chronic case reported by Stanton [*9*] was a young native man who became seriously ill with fever and bronchopneumonia. At the end of six weeks the patient was much improved. At this time a sinus appeared at the lower end of the left fibula and M. pseudomallei was cultured from the discharge. The patient was apparently well at the end of five months.

CASE III. Souchard [*35*] observed two cases in Indochina. A fifty-seven year old coolie had episodes of chills and fever for four months. There was slight cough, weakness and weight loss. Moderate splenomegaly and fever were present. In a few days moderate frequency of urination and slight albuminuria appeared. After six days of therapy with methenamine the patient became afebrile but urinary frequency persisted. Cultures of the urine were sterile during the treatment period. After the drug was discontinued low grade fever, pyuria and gram-negative bacilluria were present. Whitmore's bacillus was repeatedly

cultured from the urine, but two blood cultures were sterile.

Following the demonstration of malarial schizonts in the blood, quinine therapy was instituted. The fever and urinary findings persisted for two months. Serum agglutinins against Whitmore's bacillus, which earlier had been negative, were positive in a dilution of 1:300 by the end of the second month.

After another course of treatment with methenamine the patient became afebrile and asymptomatic. Further urine cultures were sterile. The patient was considered cured in the eighth month of his illness. Although urinary studies were incomplete, Souchard believed the patient to have had pyelonephritis.

CASE IV. The second patient of Souchard [*35*] was an eighteen month old native male infant. Fever for a period of one week was followed by an abscess of the hand. There was x-ray evidence of osteitis of the fifth metacarpal. Whitmore's bacillus was isolated from the abscess. After incision and drainage of the abscess a fistula appeared, but the child was afebrile. Treatment with local antiseptics apparently was not of benefit.

Nearly two months later fever recurred, and a small abscess appeared over the left parietal bone. An x-ray of the bone was normal, but M. pseudomallei was cultured from the lesion. Incision and drainage once again was followed by a fistulous tract to the bone. After therapy with an autogenous vaccine the patient became afebrile. At the end of six months lesions of both the skull and hand had healed and the patient was apparently cured.

CASE V. Grant [*28*] reported the case of a twenty-seven year old British soldier whose early history was complicated by what was initially thought to be gonococcic arthritis of the right hip and ankle while he was in Singapore and Malaya. After an asymptomatic interval of six months and on his return to England, bilateral bronchopneumonia developed followed by bony lesions of the right hip joint which completely subsided. The patient then had recurrent episodes of fever followed by abscesses of the malleolus, forehead and parotid gland from which Whitmore's bacillus was cultured. He later had destructive lesions of thoracic vertebrae. Sulfonamides were used intermittently, with a convincing febrile response on each occason. The patient was still ill at the time of Grant's communication, the fifth year of the disease.

CASE VI. The case reported by Mayer [*36*] was that of a thirty-two year old British soldier in Singapore in whom bilateral destructive lesions slowly developed in the sacroiliac joints. This was succeeded by collapse of the eighth thoracic vertebra and the formation of a paravertebral abscess. There was also infiltration of the right lung with bilateral hilar lymph node enlargement. The leukocyte count was 6,400 per cu. mm. with 52 per cent neutrophils; blood sedimentation rate was 110 mm./hour (Westergren). Earlier in the disease he had a leukocytosis of 17,000 per cu. mm., and blood cultures were sterile. Fever initially diminished temporarily after treatment with sulfapyridine. Although repeated studies for tubercle bacilli were negative, the patient was considered to have tuberculosis.

After a psoas abscess developed, M. pseudomallei was cultured from an aspirate of the abscess. The serum agglutination test with the organism isolated from the patient was positive in a dilution of 1:500. He continued to form abscesses and sinuses from which Whitmore's bacillus was grown despite treatment with an autogenous vaccine and local application of urea, but became afebrile with sulfadiazine. His general condition improved and all sinuses healed in the fifth year of the disease. X-ray of the patient's chest was normal, but bony lesions were still present.

CASE VII. McDowell [*5*] reported the first case from the Western hemisphere. This was a thirty-one year old white male American who had been out of the United States only once—in the Panama Canal Zone from 1927 to 1928. In 1938 the patient had a tender, dark swelling in the right buttock. A physician incised and drained the area. A few days later the patient had high fever and was unconscious for thirty-nine days. He remained in the hospital for three years and eight months, undergoing seventy-eight drainage operations for abscesses about the right buttock extending posteriorly to the knee.

Leukocytes varied from 5,000 per cu. mm. to 15,000 per cu. mm. X-ray films of the bones and the chest were normal. After M. pseudomallei was cultured from a nodule on the thigh, the patient was treated unsuccessfully with sulfadiazine, streptomycin and penicillin. He improved greatly after extensive incision, cautery and grafting of the involved area in the eighth year of his illness.

CASE VIII. The case reported by Patton [*37*] was that of a forty-six year old Dutchman who had been a prisoner of war in Siam for over three years. He had pneumonia and was also found to have malaria. A good response followed initial therapy with antimalarial drugs and sulfapyridine. However, he quickly became febrile again, had auricular fibrillation, a pericardial effusion and a right pleural effusion. Diarrhea unresponsive to emetine, a generalized petechial rash and probable suppurative arthritis of the right knee appeared later. Leukocytes were 17,500 per cu. mm. with 75 per cent neutrophils; blood sedimentation rate was 105 mm./hour (Westergren). Blood and urine cultures were sterile.

The patient died after an illness of three months in spite of treatment with penicillin and sulfapyridine for suspected subacute bacterial endocarditis. Autopsy revealed pericarditis, a spleen three times the normal size and small abscesses in the kidney and wall of the

small intestine. There was a right pleural effusion although the lung appeared to be normal. Positive cultures were obtained from the heart's blood, spleen and abscesses in the intestines and kidneys.

CASE IX. Gutner [*3*] observed a twenty-five year old American soldier in the Philippine Islands who had undergone an operation for an abscess of Meckel's diverticulum four weeks after an appendectomy. During the next year the patient lost forty-five pounds in weight and had nausea and vomiting postprandially. He then became acutely ill with a sterile right pleural effusion, cough and pain in the right side of the chest. After sulfonamide and penicillin therapy, he became afebrile, but leukocytosis (16,000 per cu. mm. to 22,000 per cu. mm.) and symptoms persisted. During the next seven months he had a low grade fever, lost weight, had pain in the right side of the chest and vomited frequently. Daily expectoration of sputum appeared, and clubbing of the fingers developed. All studies for tuberculosis were negative. Splenomegaly appeared, and a suppurative lymph node below the left mandible formed a draining sinus. Excision of this node supplied the etiologic diagnosis. M. pseudomallei was also demonstrated by guinea pig inoculation of the sputum.

During the third year of his illness the patient had a bronchobiliary fistula secondary to a ruptured abscess of the liver. His ultimate fate is not reported.

CASE X. Harries [*15*] reported one acute and four chronic cases among West African soldiers in Burma near Rangoon. His second case was a thirty-eight year old soldier who had cough, mucopurulent sputum, fever and physical signs in the right lung. Leukocytes were 12,000 per cu. mm. with 72 per cent neutrophils. During sulfonamide therapy the patient failed to improve.

In the third week of illness tender hepatomegaly and infiltration with cavitation in the upper lobe of the right lung developed. Leukocytes were 7,500 per cu. mm.; neutrophils 66 per cent. Sputum and blood cultures were negative for Whitmore's bacillus. Despite treatment with penicillin and sulfonamides the patient died after an illness lasting fifty-nine days. Autopsy showed consolidation of the right lung, with multiple abscesses 1 cm. to 6 cm. in diameter. There was slight infiltration in the left lung. Other organs were normal. M. pseudomallei was obtained from the lung abscess.

CASE XI. The third soldier reported by Harries [*15*] was thirty years old. Malaise and fever were followed by pustules on the forehead and trunk. Vesicles on the back and abscesses of the forehead, arms, knees and axilla later developed in the patient. All abscesses were subcutaneous and did not involve lymph nodes. Leukocytes were 5,400 per cu. mm.; hemoglobin, 50 per cent of normal; x-ray of the chest, negative. A positive urine culture for Whitmore's bacillus was obtained early in the disease. Later, the organism was also obtained from the abscesses.

On several occasions, treatment with sulfonamides and penicillin resulted in defervescence in a few days but new abscesses continued to form and the patient's fate is unknown. He was last seen six months after the onset of illness, still with multiple abscesses.

CASE XII. The fourth case of Harries [*15*] was a twenty-nine year old man who had cough and substernal pain with infiltration in both lungs. During the second week of illness cavitation appeared in the left lung. His irregular fever did not respond to therapy with penicillin. Leukocytes were 6,000 per cu. mm. and M. pseudomallei was cultured from the sputum in the eighth week of illness. The serum agglutination titer was 1:20 in the seventh week and 1:640 in the tenth week of illness.

The patient became afebrile and sputum cultures were negative for M. pseudomallei following treatment with penicillin and sulfonamides. However, Whitmore's bacillus was again present in the sputum after the drugs were discontinued. Following another course of therapy it was no longer possible to culture the organism. He was apparently well at the end of six months, and x-rays of the chest were normal. He was alive and well seventeen months after first becoming ill.

CASE XIII. The fifth case of Harries [*15*] was a twenty-three year old soldier who presented with fever, productive cough and slight hemoptysis. There was consolidation of the right upper lobe and questionable cavitation. During the fifth month of illness the patient was producing 6 to 8 ounces of purulent sputum daily, and there was a large, thick-walled cavity in the right upper lobe. A serum agglutination test for M. pseudomallei was positive in a dilution of 1:1,280. Later the organism was cultured from the sputum.

Since the patient failed to respond after therapy with sulfonamides and parenteral penicillin, 300,000 units of penicillin were injected through the wall of the chest directly into the lung cavity. The patient improved almost immediately, and the cavity closed completely. He was well, and the x-ray film of the chest was normal after eight months of illness.

CASE XIV. Beamer [*4*] observed a twenty-five year old white woman who had never been out of the United States. She had an undiagnosed mass in the right axilla which receded after radiation. Ten months later a large, subcutaneous abscess slowly developed in the lower part of the abdomen. This broke down and drained pus. Bilateral inguinal adenopathy was present.

The patient's condition deteriorated with spreading of the abscess, bouts of spiking fever and terminal

convulsions. She died nine months after the appearance of the abscess. She had been treated with a sulfonamide, penicillin, streptomycin and fuadin.® Postmortem examination revealed retroperitoneal necrosis with much viscid pus. The liver and kidneys showed minute foci of non-specific granulomatous inflammation. Whitmore's bacillus was obtained from postmortem cultures.

CASE XV. The case reported by Garry [*1*] is the second case from the United States. The patient was a forty-five year old white male alcoholic who had never been outside the United States. He became acutely ill with vomiting, fever and an inflamed ulcerated lesion on the right thigh. He was jaundiced, with tender marked hepatomegaly and tenderness in the right flank. There was an anemia with initial leukopenia (5,400 per cu. mm.) followed by leukocytosis of 16,000 per cu. mm. with an increase in young forms. Blood chemical determinations indicated hepatocellular damage.

The lesion on the right thigh broke down to form a raw surface with purulent exudate and later involved the scrotum and perineum. M. pseudomallei was cultured from the inguinal region and scrotum. The patient gradually improved and tests of hepatic function reverted to normal. Penicillin, streptomycin and chlortetracycline were of doubtful value. The patient was still not completely well at the end of three months.

CASE XVI. Sakihara [*27*] observed a thirty-two year old Japanese soldier in Malaya who became acutely ill with chills and fever. Grape-like clusters of vesicles and pustules appeared on the left thigh, with associated femoral adenopathy. There was tender hepatomegaly and slight jaundice. During the fifth week of illness a subcutaneous abscess of the left calf developed. Chemosis of the left eye was followed by exophthalmos and a caseous nodule on the sclera resulting in blindness. Toward the end of the illness, ascites and a pleural effusion appeared. The patient died on the ninety-fourth day of illness. Whitmore's bacillus was cultured from the left eye, femoral nodes, skin lesions, ascitic and pleural fluids and urine. Therapy consisted of a sulfonamide, arsenic, antimony, quinine and emetine.

CASE XVII. Ives [*8*] reported a forty year old white male engineer who became ill in central India. A furuncle on the right thigh healed but was followed by low grade fever, loss of weight and weakness. Hepatomegaly with collapse of the right lung base appeared. Attempted aspiration of a postulated liver abscess was unsuccessful, and laparotomy was performed. This revealed only a hard, large liver. On transfer to Glasgow during the sixth month of illness, leukocytes were 11,000 per cu. mm. and hemoglobin 12.2 gm./100 ml. Four blood cultures were sterile. Because of persistent fever (102°F. to 103°F.) and hepatic tenderness unresponsive to emetine, laparotomy was again performed. This time the liver was found to contain multiple abscesses from which M. pseudomallei was grown.

The patient died in the twelfth month of illness. Chlortetracycline, oxytetracycline (terramycin®), a sulfonamide and emetine were of no value. A slight febrile response was obtained from penicillin and streptomycin, but penicillin alone was not effective. At autopsy the abscesses of the liver were the only significant abnormality.

COMMENTS

The recorded cases of chronic melioidosis are summarized in Table I. It is apparent that all but one case occurred in men, and all except one occurred in adults. Disregarding our case, all but three of the cases occurred in the Far East or in the islands of the Pacific.

An acute illness, usually pneumonic or without localizing signs or symptoms, was the initial manifestation of two-thirds of the chronic cases. The lung was the organ more frequently involved, and cavitation was common. The liver was involved in approximately one-third of the cases. All but two of the fatal cases had hepatic lesions.

The rarity of lesions in the gastrointestinal tract is of interest when compared to their frequency in the lung. There were also few patients with gastrointestinal complaints. Perhaps this has significance regarding the portal of entry of the organism.

Involvement of the skin, the only site affected in the "afebrile" group of cases discussed earlier, was present in the form of abscesses in approximately one-half of the cases. Sinuses leading to bone or lymph nodes were present in approximately one-third of the cases.

Only three cases with splenomegaly were noted, and in one of these (Case III) it was explicable on the basis of malaria.

All cases were diagnosed by isolation of Whitmore's bacillus. Laboratory examination was helpful in several respects. In none of the cases was the leukocyte count over 22,000 per cu. mm. However, normal leukocyte counts were just as frequent as elevated ones. Counts in the vicinity of 11,000 per cu. mm. were the rule after the initial stages of the disease. The blood sedimentation rate was invariably elevated. Serum agglutination tests were positive in high dilution and a rising titer was demonstrated in each case in which multiple determinations were performed.

The follow-up period varied from two months

TABLE 1

CLINICAL FEATURES OF CASES OF CHRONIC DISSEMINATED MELIOIDOSIS DESCRIBED IN THE LITERATURE

Case (No.)	Author and Year	Sex	Age at Onset (yr.)	Extraction	Geographic Location of Infection	Acute Initial Symptom	Sites Involved					Site of Recovery of Organism	Outstanding Feature	Length of Follow-up Period	Final Outcome
							Cutaneous	Bone	Lung	Liver	Other				
I	Stanton, 1932	M	Young adult	Oriental	Malaya	+	Sinus to bone; abscess	+	..	..	.....	Sinus from bone	Sinuses to bone; skin abscesses	2 yr.	Still ill
II	Stanton, 1932	M	Young adult	Oriental	Malaya	+	Sinus to bone	+	+	..	.....	Sinus from bone	Sinus to bone	5 mo.	Cured
III	Souchard, 1933	M	57	Oriental	Indochina	?	.....	....	....	....	Spleen (?); urinary tract	Urine	Urinary infection	8 mo.	Cured
IV	Souchard, 1933	M	1½	Oriental	Indochina	+	Sinus to bone	+	..	..	.....	Sinus from bone	Sinuses to bone	6 mo.	Cured
V	Grant, 1943	M	27	English	Malaya, Singapore	..	Sinus to bone; abscess	+	+	..	.....	Skin abscess	Multiple chronic bone lesions	5 yr.	Still ill
VI	Mayer 1945	M	32	English	Singapore	..	Sinus to bone	+	+	..	.....	Sinus from bone	Multiple chronic bone lesions; lung infiltration	5 yr.	Still ill
VII	McDowell, 1947	M	31	American	United States (?)	+	Abscess	..	..	..	.....	Skin abscess	Chronic abscesses of buttock	8 yr.	Cured (?)
VIII	Patton, 1947	M	46	Dutch	Siam	+	Petechial rash	..	+	..	Small intestine; kidney; spleen; knee	Blood; spleen; kidney; intestinal wall	Miliary visceral abscesses	3 mo.	Died
IX	Gutner, 1948	M	25	American	Philippine Islands	..	Sinus to lymphnode	..	+	+	Spleen	Sputum; lymph node sinuses	Prolonged fever; bronchobiliary fistula	3 yr.	Still ill
X	Harries, 1948	M	38	African Negro	Burma	+	.....	..	+	..	.....	Lung abscess	Multiple lung abscesses	59 days	Died
XI	Harries, 1948	M	30	African Negro	Burma	+	Abscess; vesicular rash	..	..	..	Kidney	Skin abscess; urine	Subcutaneous abscesses	6 mo.	Still ill
XII	Harries, 1948	M	29	African Negro	Burma	+	.....	..	+	..	.....	Sputum	Lung cavity	17 mo.	Cured
XIII	Harries, 1948	M	25	African Negro	Burma	+	.....	..	+	..	.....	Sputum	Lung cavity	8 mo.	Cured
XIV	Beamer, 1948	F	25	American	United States	..	Abscess	..	..	+	Node; kidney	Skin abscess	Subcutaneous abscesses	19 mo.	Died
XV	Garry, 1951	M	45	American	United States	..	Abscess	..	..	?	Lymph nodes; kidney	Skin abscess	Subcutaneous abscesses	3 mo.	Still ill
XVI	Sakihara, 1952	M	32	Oriental	Malaya	+	Abscess	..	+	+	Spleen; kidney; ascites; eye	Eye; pleural and ascitic fluid; urine; lymph nodes	Skin and visceral abscesses	94 days	Died
XVII	Ives, 1953	M	40	Irish	India	..	.....	..	..	+	.....	Liver abscesses	Liver abscesses	12 mo.	Died
Our patient	1956	M	34	American	Philippine Islands (?) or United States (?)	+	Sinus to bone	+	+	+	.....	Sinus to bone; rib	Lung and liver abscesses	10 yr.	Still ill
Summary															
		M, 17 F, 1	Child, 1 Adult, 17	Caucasian..... 9 Oriental..... 5 African Negro.... 4	East..... 13 United States.... 4 Philippine Islands. 1	12	Node..... 1 Bone..... 5 Subcutaneous. 7	6	10	6	Spleen.. 4 Kidney.. 4 Nodes... 1 Eye..... 1 Ascites.. 1	Bone..... 5 Urine..... 2 Sputum..... 3 Liver..... 1 Skin..... 5 Pleural fluid.... 1 Ascitic fluid..... 1 Eye..... 1 Intestinal wall.. 1	.....	59 days to 10 yr.	Died.... 5 Cured... 6 Still ill... 7

in the fatal Case x to eight years in McDowell's patient. Our patient is being observed in the tenth year from the onset of pulmonary symptoms.

All the reported "afebrile cases" were living, but all were obviously not well at the time they were reported. Of the seventeen systemic cases six patients were apparently cured (Cases II, III, IV, VII, XII, XIII), six were still ill (Cases I, V, VI, IX, XI, XV), and five were dead (Cases VIII, X, XIV, XVI, XVII) at the time of their report. The duration of life varied from fifty-nine days (Case X) to nineteen months (Case XIV) in the fatal cases.

TREATMENT

Therapy in melioidosis has consisted of incision of abscesses, excision of severely infected tissue, autogenous vaccine, urea, sulfonamides and antibiotics.

Early incision and drainage of abscesses are indicated [*36*] but this alone is seldom curative. It may be dangerous without concomitant antibiotic therapy, as in the case reported by McDowell [*5*]. McDowell's patient responded to wide excision and grafting of the involved tissues. Apparent cures following the development of draining sinuses are not infrequent [*9,11*], especially in the "afebrile cases." The cold abscess of our patient was not resolved by antibiotics but required incision and drainage. Although prolonged antibiotic therapy was not administered, the lung abscesses failed to respond to short-term therapy and were excised.

Autogenous vaccines have rarely been of real value when used alone [*8,9,12,36*], and urea has not been shown to be useful [*8*].

In most instances penicillin failed to alter the course of the disease [*1,2,4,5,8,15*]. However the amounts used were small since the drug was precious during the time that most of the cases were reported. In the fifth case reported by Harries [*15*] the patient failed to respond to parenteral penicillin but dramatic improvement followed instillation of the drug directly into the lung abscess. This suggests that the antibiotic may be employed successfully if high concentrations are attained at the major site of infection. Our case responded convincingly each time penicillin was administered, but allergy precluded its further use.

Only one case is available in which streptomycin appeared to affect the disease significantly [*8*]. In other instances it was disappointing [*1,4,5*].

Chlortetracycline [*1,8*] and oxytetracycline [*8*] have been ineffectual. Ours is the only report in which tetracycline has been tried. Chlortetracycline was definitely of value to our patient, but it was impossible to evaluate tetracycline because of the concomitant use of gantrisin® and chloramphenicol.

Sulfonamides are of definite value. They were apparently curative in the fourth case reported by Harries [*15*]. The patient reported by Green [*11*] was apparently cured of suppurative cervical adenitis by treatment with sulfapyridine. Gratifying febrile responses are mentioned frequently in the literature [*4,11,28,36*], but in other instances no benefit has been noted [*3–5,8,15,27*].

Our case is the only report in which chloramphenicol has been used. Much of the credit for our patient's recovery is apparently due to the use of this drug over a prolonged period of time.

Fuadin [*4,27*], arsenicals [*27*], emetine [*8*] and antimalarials [*4,27*] have been valueless.

Experimentally, streptomycin, penicillin [*38*] and chlortetracycline [*39*] have been effective. In contrast, sulfadiazine [*38*] administered early in the disease prevents death from infection in hamsters. Prolonged treatment for several weeks effectively increased survival rates. Miller et al. [*38*] suggest that prolonged treatment is necessary to eradicate foci in the tissues.

Sensitivity tests *in vitro* of organisms isolated from patients have shown much variation [*2,3,8,11,39*]. In general, resistance is present to penicillin, streptomycin and chlortetracycline. The bacteria are usually sensitive to sulfonamides [*2,8,11*]. The organism from Ives' patient [*8*] was sensitive to chloramphenicol. The bacterium from our patient was sensitive to chlortetracycline, oxytetracycline, tetracycline and chloramphenicol. Nearly all the reported sensitivity tests were performed only after the patient had received therapy, as is true in our case.

Perhaps one of the reasons that antibiotics have not been successful in melioidosis is that the diagnosis is frequently delayed until the patient is moribund or has extensive disease. Another reason may be the small doses and short courses of therapy given. In many of the reports in which sulfonamides were used the drugs were given for short periods of time due to the toxicity of the earlier preparations, and the effect of the drugs is therefore difficult to evaluate.

We believe the suggestion of Miller [*38*]

advocating prolonged therapy is of great value. Certainly in a patient with multiple metastatic foci, such as ours, long-term administration of antibiotics is indicated. Our case illustrates the possible toxic effects of such prolonged use of chloramphenicol. Even though our patient is asymptomatic it is likely that the infection is not cured.

SUMMARY

Chronic systemic melioidosis presents a diagnostic and therapeutic problem. A patient is reported in whom the disease was possibly contracted in the United States. The prolonged course in this patient is the longest on record. What was probably retrobulbar optic neuritis due to chloramphenicol appeared.

A review of previously reported cases of chronic melioidosis reveals the varied clinical features of this illness. The disease may be more common in the United States than has been recognized but thus far there are only three reported cases from this country.

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Hageman Trait (Hageman Factor Deficiency)*

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DEFICIENCY of another plasma thromboplastin precursor (Hageman factor, HF) has recently been described and the clinical entity named Hageman trait (HT), after the patient in whom the abnormality was first recognized [*1,2*]. HT is characterized by the absence of abnorma clinical bleeding despite the presence of a moderately severe coagulation defect. To date only three reports totaling six patients with HT have been published [*1–4*]. In this report another patient with HT, and studies on the physicochemical characteristics of this new factor (HF), are presented.

CASE REPORT

J. R. of German-Irish-French descent, was a twenty-six year old schoolteacher. She was in essentially good health and in the initial month of her first pregnancy when originally seen at the Washington University School of Medicine in February, 1956. She had never had abnormal bleeding or bruising and menses were always normal. She was first told she had a coagulation defect at the age of five when a routine clotting time prior to tonsillectomy was found to be five hours; the operation was cancelled. Between the ages of twelve and fifteen she was studied elsewhere and again found to have a prolonged clotting time, which became shorter during menses. At the age of seventeen an emergency appendectomy was performed without excessive bleeding and no blood transfusions were required. A tonsillectomy and adenoidectomy were performed at the age of twenty without unusual bleeding. At that time mixture studies of the patient's and "hemophiliac" blood were said to be mutually corrective. Both of the patient's parents were also studied at that time and found to have normal coagulation times.

The past history was significant in that several episodes of polyarthritis resembling rheumatic fever occurred throughout the patient's childhood up to the age of twenty.

Except for evidences of a mild upper respiratory infection, the physical examination was within normal limits. The vital signs were normal and the lymph nodes, liver and spleen were not enlarged.

The following laboratory studies were normal: urinalysis, cardiolipin test, complete blood count, hematocrit, cephalin cholesterol flocculation test, thymol turbidity test, serum bilirubin, serum cholesterol, alkaline phosphatase, serum calcium and phosphorus, total protein, albumin, globulin and paper electrophoretic analysis of serum proteins.

MATERIALS AND METHODS

Venous blood was collected through an 18-gauge needle in glass or siliconized tubes and anticoagulated with 1.34 per cent sodium oxalate (one part oxalate to nine parts blood). The plasma was separated by centrifugation at 2,500 r.p.m. for fifteen minutes at 4°C. Normal serum was allowed to incubate forty-eight hours at 37°C. in sterile glass tubes before use. Calcium chloride was used in 0.025 M. concentration for plasma and serum prothrombin determinations and in 0.2 M. concentration for plasma recalcification times. Rabbit brain thromboplastin (permaplastin) was used throughout. Bovine thrombin (Upjohn Co.) was dissolved in veronal buffer (pH 7.35). All clotting studies except the siliconized tube clotting times were carried out in 11 by 100 mm. glass tubes at 37°C. unless otherwise specified.

Clotting Time. Through an 18-gauge needle, after discarding the first few milliliters, approximately 2 ml. of blood were allowed to flow directly into two glass tubes and 7 ml. into two 14 by 125 mm. siliconized glass tubes and allowed to clot.

Twenty-four-hour Serum Prothrombin. Blood was allowed to clot in a sterile glass tube and the serum incubated at 37°C. for twenty-four hours. One-tenth ml. of the serum was added to 0.1 ml. normal barium sulfate-treated plasma, 0.1 ml. thromboplastin and 0.1 ml. calcium chloride and the clotting time determined.

Thromboplastin Generation Test. The method of Biggs and Douglas [*5*] was employed. Plasma was treated with barium sulfate instead of $Al(OH)_3$.

Thrombin Time. One-tenth ml. of bovine thrombin (6.6 μ./ml.) was added to 0.4 ml. of plasma and the clotting time determined.

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TABLE I
ROUTINE COAGULATION STUDIES

Data	Results	Normal Values
Platelet count (Dameshek)	457,000	300,000–900,000/cu. mm.
Rumpel-Leede test	Negative	
Bleeding time (Ivy)	6½ minutes	Less than 10 minutes
Coagulation time		
Glass tube	60 minutes	Less than 15 minutes
Siliconized tube	60–150 minutes	Less than 120 minutes
Clot retraction	Normal	
Prothrombin time (Quick)	14.1 seconds	12–14 seconds
Twenty-four-hour serum prothrombin	8–10 per cent	Less than 15 per cent
Thromboplastin generation test	Abnormal	
Thrombin clotting time	15 seconds	15–17 seconds
Fibrinogen	330 mg. per cent	200–400 mg. per cent
Fibrinolysis	No gross clot lysis	

Fibrinogen Concentration. The method of Ratnoff [6] was employed.

Fibrinolysis. Blood was allowed to clot in a sterile tube and observed for fibrinolysis up to forty-eight hours.

Plasma Recalcification Time. Plasma recalcification times were performed on fresh or, when indicated, frozen plasmas at 27 to 29°c. (plasmas rendered platelet-poor by centrifugation at 3,300 r.p.m. at 4°c. for thirty minutes and stored frozen no more than six weeks before use).

RESULTS

Routine Coagulation Studies. The results of routine coagulation studies are listed in Table I. The platelet count, Rumpel-Leede test, bleeding time, clot retraction, prothrombin time (one-stage), twenty-four-hour serum prothrombin, thrombin time and fibrinogen concentration were all normal. No gross fibrinolysis was evident. The clotting time was markedly prolonged in glass but only slightly prolonged in siliconized tubes. Serum prothrombin levels determined serially during and for several hours following clotting of the patient's whole blood revealed normal prothrombin consumption in glass, but slightly impaired consumption in siliconized tubes after clot formation. (Fig. 1.) On other occasions, however, slightly impaired prothrombin consumption was noted in glass tubes four hours after clotting had occurred.

Exclusion of a Circulating Anticoagulant. Circulating anticoagulant appeared to be excluded by the failure of one part of the patient's plasma to prolong the recalcification time of nine parts of normal plasma and by the capacity of one part of normal plasma to correct the prolonged recalcification time of nine parts of the patient's plasma.

Demonstration of Deficiency of a Plasma Clotting Factor. The addition of one-tenth the volume of normal plasma, plasma treated with barium sulfate and serum to the patient's plasma resulted in correction of the patient's prolonged recalcification time. (Table II.) The patient's plasma was presumed to be deficient in a clotting factor present in normal plasma, plasma treated with barium sulfate, and serum.

Localization of the Defect to the Early Stage of Coagulation (Thromboplastin Formation). The normal second (prothrombin time) and third (thrombin time, fibrinogen concentration) stages of coagulation placed the abnormality in the early or initial stage of coagulation, i.e., stage of plasma thromboplastin formation. A thromboplastin generation test confirmed the impaired formation of thromboplastin. (Fig. 2.) Both the patient's barium sulfate-treated plasma and serum were required to demonstrate the defective formation of thromboplastin in the thromboplastin generation test. Similar thromboplastin generation curves have been described in plasma thromboplastin antecedent (PTA) and HF deficiencies [4,7]. The plasmas of patients deficient in antihemophilic globulin (AHG), plasma thromboplastin component (PTC) and Spaet's plasma thromboplastin factor-D (PTF-D) [8] exhibit thromboplastin generation curves unlike that observed in this study.

Demonstration of the Capacity of the Patient's Plasma to Correct the Prolonged Plasma Recalcification

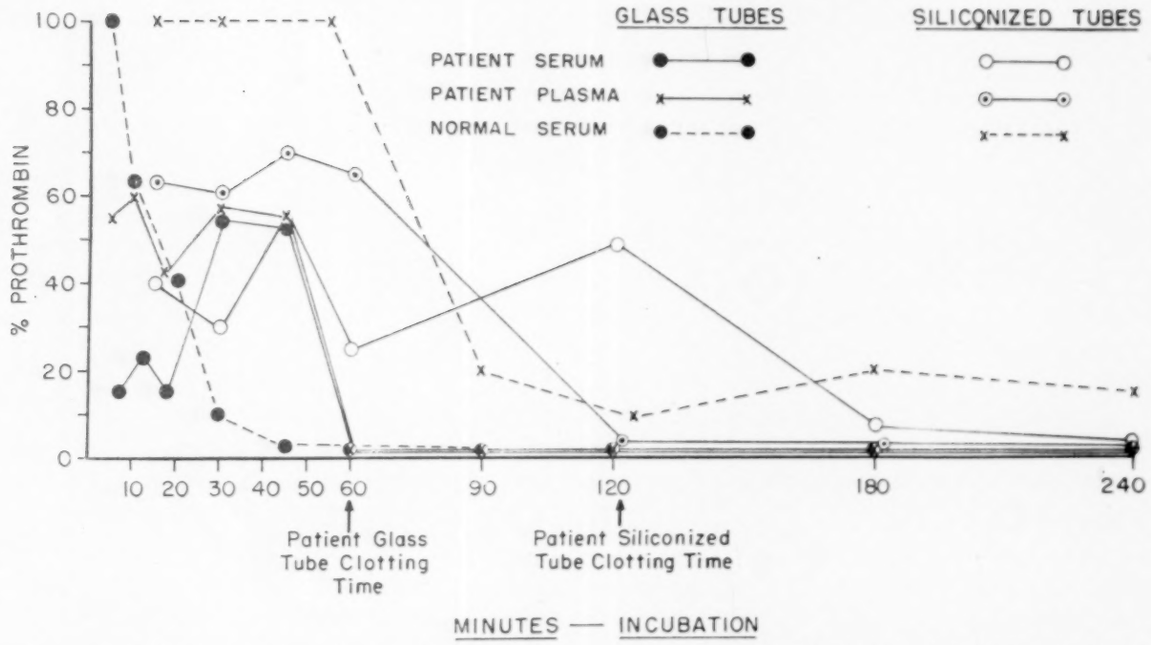


FIG. 1. The plasma and serum prothrombin levels determined during coagulation of the patient's whole blood. Two ml. of the patient's whole blood collected in a siliconized syringe were placed in glass tubes and 5 ml. in 14 by 125 mm. siliconized tubes and allowed to clot. At the intervals indicated the coagulation process was arrested with 3.8 per cent sodium citrate (one part citrate to nine parts blood). Approximately four hours after the blood had been placed in the tubes the citrated mixtures were separated by centrifugation and the plasma and serum prothrombin levels determined.

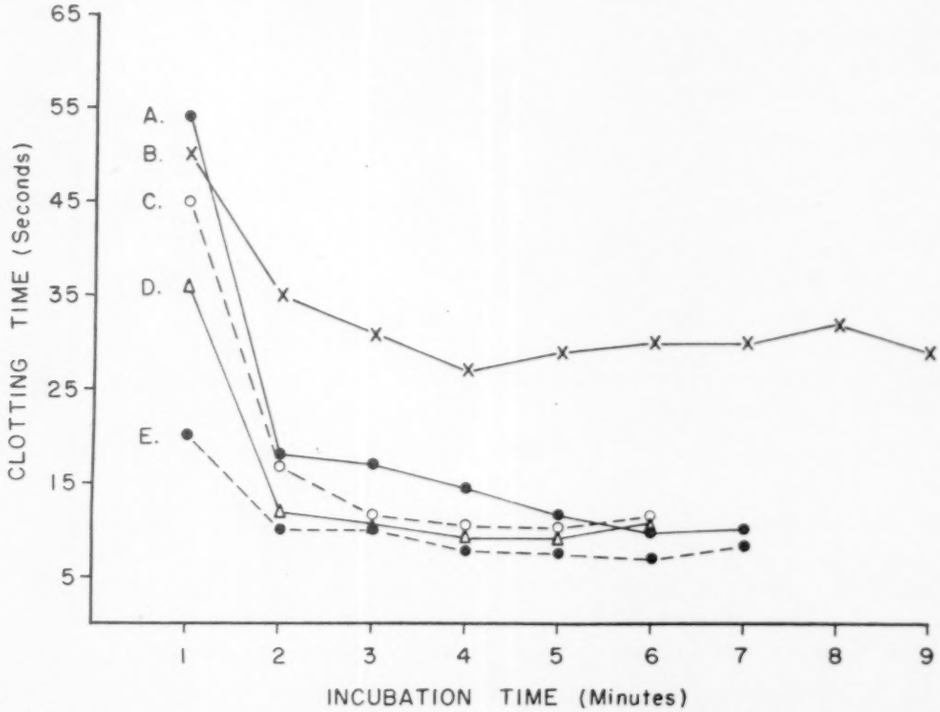


FIG. 2. The effect of substitution of the patient's reagents in the thromboplastin generation test. (a) All normal reagents. (b) Patient's barium sulfate-treated plasma and serum substituted. (c) Only patient's serum substituted. (d) Only patient's barium sulfate-treated plasma substituted. (e) Only patient's platelets substituted.

Time of Patients Deficient in AHG, PTC and PTA. The addition of one-tenth the volume of the patient's plasma to plasmas from patients deficient in AHG, PTC and PTA resulted in significant correction of the prolonged recalcification times of the latter. (Table III.) The patient's plasma appeared to contain adequate quantities of AHG, PTC and PTA factors.

TABLE II

EFFECT OF NORMAL PLASMA, $BASO_4$-TREATED PLASMA AND SERUM ON THE PROLONGED RECALCIFICATION TIME OF THE PATIENT'S PLASMA

Data	Clotting Time (min.)
Saline solution	16
Normal plasma	4½
Normal $BaSO_4$-treated plasma	6¾
Normal serum	3½
Normal control recalcification time	3½

NOTE: To 0.9 ml. of the patient's plasma, 0.1 ml. of the following plasmas, serum or saline solution were added and the mixture recalcified with 0.1 ml. $CaCl_2$.

Correction of the Patient's Prolonged Plasma Recalcification Time by Plasmas Deficient in AHG, PTC, PTA and PTF-D, but Failure of Correction by HF-Deficient Plasma. The addition of one-tenth the volume of plasma from patients deficient in AHG, PTC, PTA and PTF-D* factors to the patient's plasma resulted in significant correction of the patient's prolonged recalcification time while HF-deficient plasma † failed to provide any correction. (Tables IV and V.) Plasmas from patients lacking AHG, PTC, PTA and PTF-D factors appeared to contain clotting factors capable of correcting the prolonged plasma recalcification time of the patient. However, plasma from a patient deficient in HF and the patient's plasma appeared mutually deficient in a clotting factor necessary for normal formation of plasma thromboplastin, at least *in vitro*.

Effect of Glass Surface on the Patient's Whole Blood and Plasma Recalcification Clotting Times. One ml. of the patient's whole blood placed in glass tubes varying in diameter from 8 to 16 mm. coagulated more rapidly in the smaller than in the larger diameter tubes. The exposure of the patient's whole blood to more glass surface did not increase the coagulation time.

TABLE III

CORRECTIVE EFFECT OF PATIENTS PLASMA ON PROLONGED RECALCIFICATION TIMES OF PLASMAS DEFICIENT IN AHG, PTC AND PTA

Plasmas	Clotting Time (min.)	
	Patient's Plasma Added	Saline Solution Added
AHG-deficient plasma	7	25
PTC-deficient plasma	5	18½
PTA-deficient plasma	7	28
Normal control recalcification time	..	5

NOTE: To 1.0 ml. of the plasmas (kept frozen before use) deficient in AHG, PTC and PTA, 0.1 ml. of the patient's plasma and a corresponding 0.1 ml. saline solution control were added and the mixtures recalcified with 0.1 ml. $CaCl_2$.

Collection and preparation of the patient's plasma in siliconized glassware, at no time in contact with glass, still resulted in an abnormal clotting time when the plasma was recalcified in siliconized tubes.

Quantitative Evaluation of the Minimum Amount of Normal Plasma Necessary to Correct the Patient's Prolonged Plasma Recalcification Time. Extremely minute amounts of normal plasma (one part normal plasma to 3,200 parts of the patient's plasma) significantly shortened the prolonged plasma recalcification time of the patient. (Fig. 3.) In contrast plasmas from patients lacking AHG and PTC required larger amounts of normal plasma to shorten their plasma recalcification times (one part normal plasma to 10 to 100 parts of the patient's plasma). However, one AHG-deficient plasma showed slight correction with one part normal plasma to 400 and 1,600 parts of the patient's plasma. In a patient with

* PTF-D deficient plasma was generously supplied by Dr. T. H. Spaet, Montefiore Hospital, New York, N. Y.

† Lyophilized HF-deficient plasma was kindly supplied by Dr. O. D. Ratnoff, Western Reserve University School of Medicine, Cleveland, Ohio. The patient's frozen plasma was originally sent to Dr. Ratnoff who observed the failure of the patient's plasma to correct the prolonged recalcification of a HF-deficient plasma: ". . . patient's recalcified plasma clotting time fifty-six minutes, HF-deficient plasma recalcified clotting time thirty-three minutes, recalcified time of equal mixtures of the patient's and HF-deficient plasmas thirty-one minutes, recalcified time of patient's plasma plus 1/40 normal plasma ten minutes, and recalcified time of HF-deficient plasma plus 1/40 normal plasma six minutes."

HT reported elsewhere [*4*], as little as 50 ml. of twenty-day old normal blood administered intravenously corrected the coagulation defect for a period of thirty-six hours.

Family Studies. Coagulation studies in the patient's parents were essentially normal (studies performed as in Table I, except for fibrinogen concentration and thrombin time). Fourteen other family relatives (seven males and seven females) were not available for study but none, including the parents gave any history of abnormal bleeding tendency.

TABLE IV
EFFECT OF PLASMAS FROM PATIENTS DEFICIENT IN AHG, PTC, PTA AND HF, AND PLASMA FROM THE PATIENT'S FATHER ON PROLONGED RECALCIFICATION TIME OF PATIENT'S PLASMA

Plasmas	Clotting Time (min.)
Saline solution	18
AHG-deficient plasma	5
PTC-deficient plasma	7
PTA-deficient plasma	6½
HF-deficient plasma*	24
Plasma from patient's father	8
Normal control recalcification time	4½

NOTE: To 1.0 ml. of the patient's plasma, 0.1 ml. of the plasmas were added and the mixtures recalcified with 0.1 ml. $CaCl_2$.

* One ml. lyophilized HF deficient plasma reconstituted in 1 ml. saline.

PHYSICOCHEMICAL PROPERTIES OF HF

HF was present in normal plasma, in barium sulfate-treated normal plasma, and in normal serum and was not dialyzable from plasma or serum or from fractions of normal plasma obtained by ammonium sulfate precipitation.

Heat Stability. Heating normal plasma at 65°C. for fifteen minutes completely destroyed HF activity; however, HF resisted heating at 60°C. for fifteen minutes. Barium sulfate-treated normal serum heated at 56°C. for thirty minutes exhibited no reduction in HF activity.

Ammonium Sulfate Fractionation. HF was found in all precipitates obtained from normal plasma by ammonium sulfate fractionation. Slight activity was found in the fraction obtained by 0 to 25 per cent saturation with ammonium sulfate. Maximal activity was found in the 25 to 33 and 33 to 50 per cent precipitates, the latter being slightly more active.

Cohn's Plasma Fractions. HF was found mainly in Cohn's plasma fractions III, IV-1 and IV-4.*

Electrophoretic Localization in Serum. Normal serum was separated by paper electrophoresis, the paper cut into strips and the protein fractions were eluated from each strip with saline solution. HF was found to be present mainly in the area between the beta and gamma globulins. Slight activity was also found in the beta globulin fraction.

TABLE V
CORRECTIVE EFFECT OF PTF-D (SPAET) DEFICIENT PLASMA ON PROLONGED PLASMA RECALCIFICATION TIME OF PATIENT

Plasmas	Clotting Time (min.)
Saline solution	50
PTF-D deficient plasma	9
Normal plasma	12
Normal control recalcification time (frozen)	13

NOTE: To 1.0 ml. of the patient's plasma (kept frozen before use), 0.1 ml. of the plasmas were added and the mixtures recalcified with 0.1 ml. $CaCl_2$.

Activity in Dicumarolized Plasma and the Newborn. Plasma from a patient receiving dicumarol (prothrombin activity of 14 per cent) and from a newborn did not show reduction in HF activity.

COMMENTS

Clinical Features. HT is clinically characterized by a striking absence of abnormal bleeding tendency despite the presence of a moderately severe coagulation defect. Even surgical procedures such as dental extractions, tonsillectomy, adenoidectomy, appendectomy, hemorrhoidectomy, ovariectomy, removal of a sebaceous cyst and repair of a varicocele have not been associated with abnormal bleeding. In addition, abnormal bleeding has not occurred with gunshot wound, menses or childbirth. Because of the lack of hemorrhagic manifestations, patients with HT have been discovered accidentally, usually as a result of a routine preoperative coagulation time. The typical clinical features

* Supplied by the American National Red Cross, National Headquarters, Washington, D. C. through the courtesy of Dr. J. N. Ashworth.

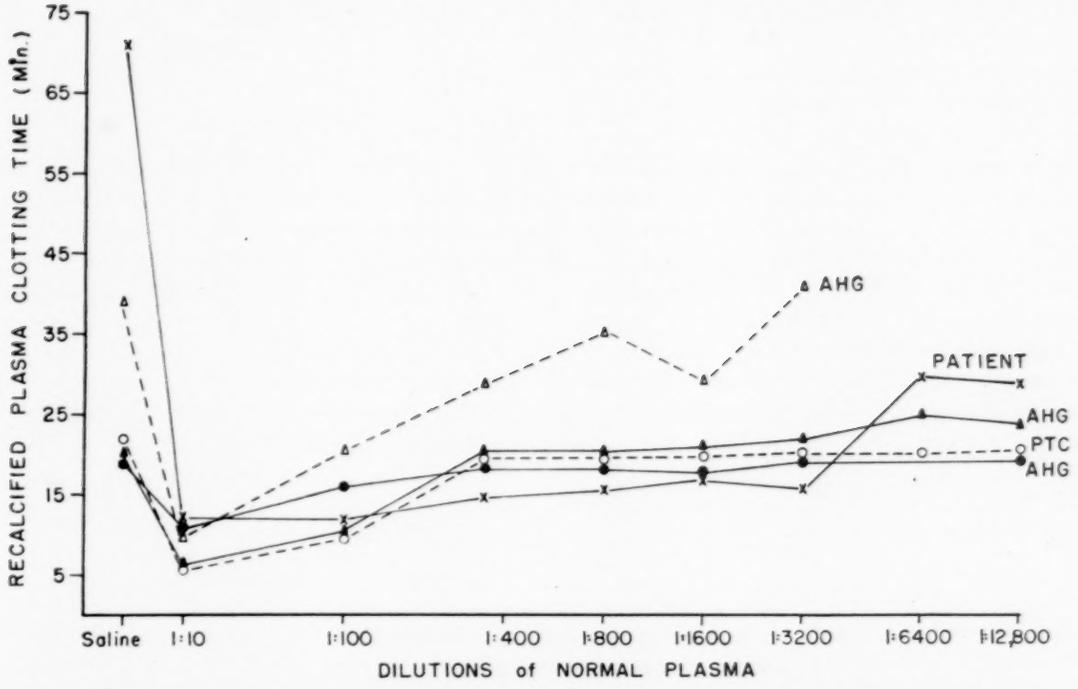


FIG. 3. Measurement of the smallest amount of normal plasma necessary to reduce the prolonged plasma recalcification of the patient. Normal plasma was serially diluted with saline solution and 0.1 ml. of the diluted plasma added to 1.0 ml. of the patient's plasma (kept frozen before use). The mixture was recalcified with 0.1 ml. $CaCl_2$. Similar determinations were carried out on plasmas from patients deficient in AHG and PTC.

of HT were presented by the patient reported, including the absence of spontaneous abnormal bleeding, the lack of pathologic bleeding after tonsillectomy and appendectomy, and the discovery of the coagulation defect as the result of a routine preoperative coagulation time.

Hereditary Aspects. The occurrence of HT in both sexes suggests the lack of a sex-linked inheritance pattern and probable dominance of the carrier gene. The few family studies in HT have not been adequate to define the exact hereditary pattern. The disease, however, does not appear to be directly inherited. HT has been reported in two sibling sisters but investigation of fifteen other members of the family disclosed no coagulation abnormalities [*1*]. In the only other family study of a patient with HT, two children and two grandchildren of the patient exhibited no coagulation defect [*4*]. Both parents of the patient in this report exhibited normal coagulation.

A common racial denominator may be apparent in HT. Four of the patients with HT, including the reported case, have German ancestors [*1,2*], while another was of Lithuanian descent [*4*], a national group closely related to the Germans. However, the three patients of German descent reported elsewhere were not directly related to the patient in this report [*9*]. Consanguinity has been found in one of the reported patients with HT [*10*].

Of interest is the discovery of the five-hour coagulation time at the age of five in the patient reported. The other published cases of HT have been discovered in adulthood. The diagnosis of the coagulation defect early in childhood suggests the probable presence of the abnormality since birth.

Nature of the Coagulation Defect. The essential defect in HT appears to be a deficiency of another plasma thromboplastin precursor (HF) distinct from AHF, PTC, PTA, PTF-D and factor X [*11*]. Plasmas of patients deficient in AHG, PTC, PTA and PTF-D apparently contain adequate amounts of HF while normal quantities of AHG, PTC, PTA and PTF-D appear to be present in plasmas of patients with HT. Plasmas deficient in HF are corrected, at least *in vitro*, by the addition of normal plasma, barium sulfate-treated plasma and serum, and by the addition of plasmas deficient in AHG, PTC, PTA and PTF-D. Plasmas from patients

with HT mutually fail to correct the defect of each other, although capable of correcting the plasma coagulation defect of the other known thromboplastin precursor deficiencies. Factor X is markedly absorbed by barium sulfate, is relatively heat labile (being denatured by heating at 56°c.) and is decreased in epidemic hepatitis, cirrhosis, newborns and marcoumar (dicumarol derivative)-treated patients [*11*]. HF does not appear identifiable with another recently postulated factor necessary for normal thromboplastin generation [*12*].

The prolonged coagulation time in glass but only slightly prolonged coagulation time in siliconized tubes in the patient reported remains unexplained. The data would suggest, however, that HF is not absorbed out or inactivated by exposure to glass surface.

Although the patient's whole blood coagulation time was markedly prolonged in glass, the rapid consumption of residual prothrombin once coagulation had occurred would suggest the defect to be due to a delay in rate of thromboplastin formation rather than in the quantity of thromboplastin formed.

Physicochemical Properties of HF. HF is found in normal plasma and serum and is only slightly absorbed by barium sulfate [*9*]. Of all the known plasma thromboplastin precursors, HF appears to be the most resistant to heating, an observation confirmed in this study.

HF may be found in all ammonium sulfate fractionated precipitates of normal plasma [*4*], but mainly in the 25 to 33 per cent [*3*] and 25 to 40 per cent precipitates [*1,2*]. Studies in this report support these observations, revealing maximal activity in the 25 to 33 and 33 to 50 per cent precipitates.

Published data on the presence of HF in Cohn's plasma fractions is scanty. Earlier studies suggested that both fractions II and III contained HF activity [*2*]. More recent studies, however, have disclosed HF act vity mainly in fraction III [*9*]. In this study HF activity was found in fraction III, but also in fractions V-1 and IV-4.

HF has been reported to be a globulin migrating electrophoretically between the beta and gamma globulins [*3,9*]. Similar observations were made in this study; HF was found mainly confined to this area. The slight activity in the beta globulin observed in this study may have been due to activity of this component or contamination from the adjacent active area due to incomplete separation of the components.

Dicumarol administration does not appear to depress HF or AHG [*13*] activity but may reduce PTC and factor X activity [*11,14*]. HF seems to be present in adequate amounts in newborn plasma, while PTC and factor X may be reduced [*11,15*]. No information is available on PTA and PTF-D levels during dicumarol administration or the levels of PTA and PTF-D in the newborn.

The Lack of Abnormal Clinical Bleeding in HT. Why patients with HF deficiency fail to show abnormal hemorrhagic manifestations remains unexplained. Hemostasis is apparently adequate *in vivo* yet abnormal *in vitro*. Possibly tissue thromboplastin in patients with HT may be sufficient to insure normal hemostasis *in vivo* despite deficiency of HF.

SUMMARY

The seventh case of HT is reported, of a twenty-six year old woman of German-Irish-French descent in whom abnormal clinical bleeding was absent despite the presence of a severe coagulation defect discovered at the age of five. Coagulation studies of the patient's parents were normal. Fourteen family relatives gave no history of abnormal bleeding. The coagulation defect consisted of a prolonged coagulation time in glass, but only slightly prolonged time in siliconized tubes. The patient's barium sulfate-treated plasma and serum combined produced an abnormal thromboplastin generation test. The patient's prolonged plasma recalcification time was corrected by normal plasma in extremely minute amounts by barium sulfate-treated plasma, by serum and plasmas deficient in AHG, PTC, PTA and PTF-D, but not by plasma deficient in HF. The patient's plasma corrected the prolonged plasma recalcification times of AHG, PTC and PTA-deficient plasmas. HF present in plasma and serum was found to be non-dialyzable, poorly absorbed by barium sulfate, resistant to heating at 60°c. for fifteen minutes, present in the 25 to 33 and 33 to 50 per cent ammonium sulfate fractionated normal plasma precipitates, present in Cohn's plasma fractions III, IV-1 and IV-4, to migrate electrophoretically between the beta and gamma globulins and not to be decreased by dicumarol administration or in the newborn.

Acknowledgment: The authors are indebted to Doctor E. H. Reinhard for permission to study

and report this case and to Doctor Carl Moore for his helpful advice and criticism.

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Resuscitation from Cardiac Arrest Due to Digitalis by External Electric Stimulation*

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SYNCOPE due to digitalis intoxication is uncommon. Just as in cardiac syncope from other causes the cardiac mechanism causing the seizures may be ventricular standstill, tachycardia or fibrillation. Although serious cardiac toxicity from digitalis is usually manifested by ectopic ventricular activity or by depression of atrioventricular conduction, depression of sinoatrial impulse formation may also occur in the form of sinoatrial bradycardia, pauses, block or standstill [*1,2*]. If a lower atrioventricular or ventricular pacemaker does not escape during sinoatrial standstill, syncope or sudden death may result.

We have developed a new therapeutic approach to the problem of ventricular standstill: an externally applied cardiac pacemaker that stimulates the heart electrically, terminates ventricular standstill and maintains an externally paced ventricular rhythm for as long as necessary. Resuscitation by this technic has been applied successfully in Stokes-Adams disease, reflex vagal standstill, unexpected cardiac arrest in the operating room and in standstill due to administration of procaine amide [*3,4*].

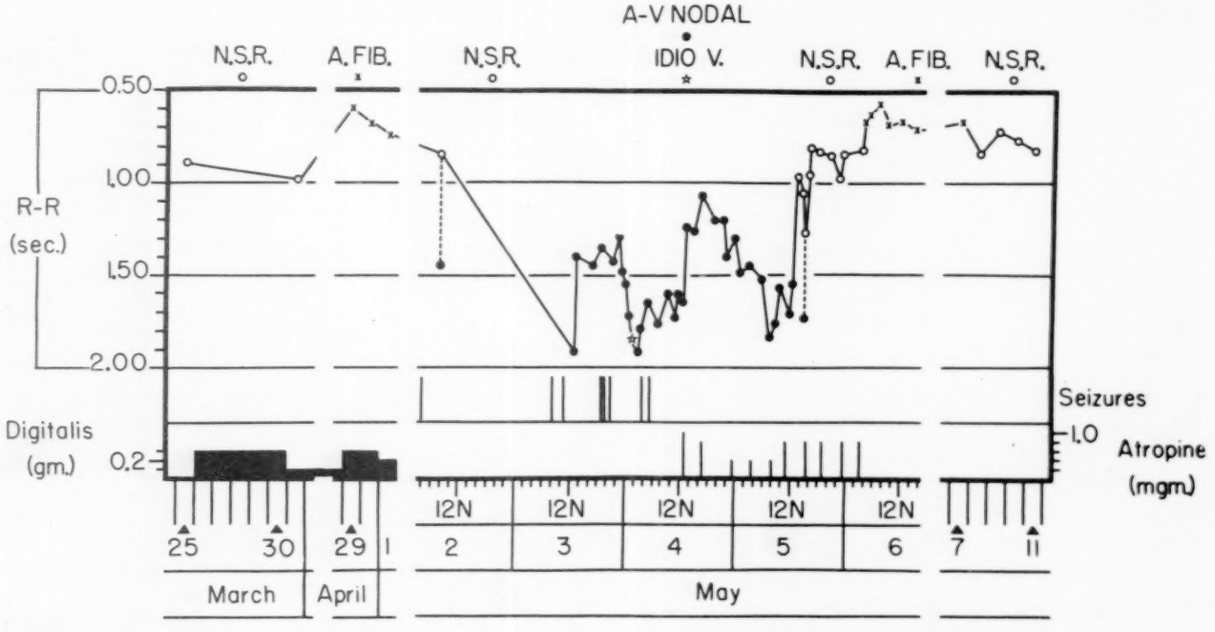


FIG. 1. The sequence of arrhythmias, the ventricular rates, and the syncopal attacks are shown in their temporal relations to the administration of digitalis and atropine.

Here we are reporting a case of cardiac syncope due to digitalis intoxication in which episodes of cardiac standstill were terminated by external electric stimulation of the heart.† The

† We have avoided the term Stokes-Adams attacks in this case and have used what we consider to be the more appropriate term, cardiac syncope due to cardiac stand-

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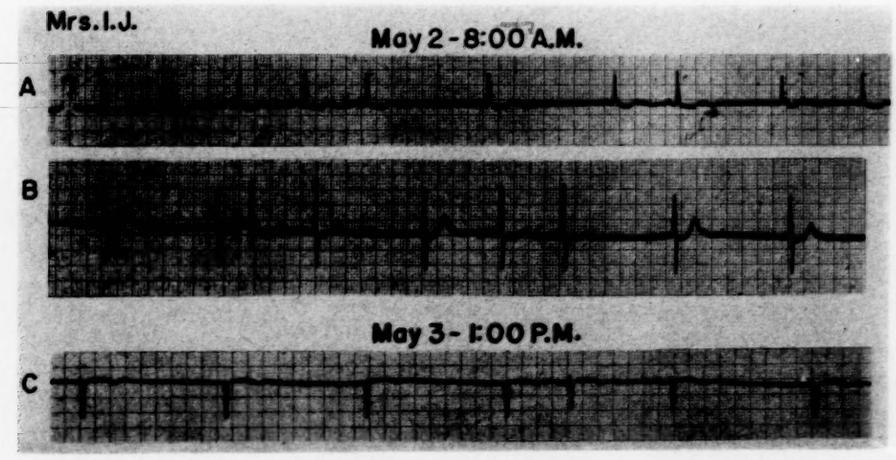


FIG. 2. Electrocardiograms on May 2 and 3 showing increasing interference with sinoatrial impulse formation and increasing predominance of the A-V node. A, lead I shows 5 sinoatrial beats (R-R 0.86 and 0.82) followed by two cycles of sinoatrial block at twice the interval (R-R 1.60 and 1.64). The next sinoatrial cycle is normal and is followed after a long pause by an A-V nodal escape beat. B, lead V_3, a minute or so later, shows a mixture of sinoatrial and A-V nodal beats. The third complex is a premature ventricular beat. C, lead V_1 shows A-V nodal rhythm interrupted by 2 sinoatrial beats. The sinoatrial cycle has lengthened to 1.33 seconds.

value of atropine in accelerating depressed cardiac pacemakers is also clearly documented.

CASE REPORT

Mrs. I. J., a seventy year old white woman, was admitted to the Beth Israel Hospital on May 3, 1955, because of syncopal attacks during the preceding thirty-six hours. She had been well except for generalized arthritic pains, hypertension of 220/90 mm. Hg, and occasional dyspnea and dizziness on exertion.

She also complained of palpitation one and a half months prior to admission. Her blood pressure was 220/104 mm. Hg and the electrocardiogram revealed frequent atrial premature beats and left ventricular hypertrophy. Because of persistent palpitation, she received 1.5 gm. of digitalis over a five-day period (Fig. 1, March 26 to 30) and was then given a daily maintenance dose of 0.1 gm. (Fig. 1, March 31 to April 28.)

On April 29 she complained of continuous palpitation of several days' duration, anorexia, weakness on walking, and one "weak spell." Her cardiac rhythm was totally irregular and she appeared clinically to have atrial fibrillation, so the digitalis dosage was increased.

On May 2 she fainted and was thought to have had a convulsion. The blood pressure was 180/90 mm. Hg and the pulse was irregular, varying between 64 and 70. There were no other significant physical findings. An electrocardiogram (Figs. 2A and B) revealed basic normal sinus rhythm with normal P-R interval interrupted by intermittent sinoatrial block with nodal escape beats. The digitalis was therefore omitted. The next day she was nauseated, vomited and had two syncopal attacks. The heart was irregular and slow at 44 beats per minute. She was then admitted to the hospital.

On admission she appeared pale and moderately dehydrated. The blood pressure was 140/40 mm. Hg, the respirations were 20 per minute, and the pulse was 36 and irregular. The heart was slightly enlarged and there were faint apical and basal systolic murmurs. There was no evidence of congestive failure. The hemoglobin was 12.2 gm. per cent and the white blood count was 11,700 per cu. mm. An electrocardiogram (Fig. 2C) revealed predominant atrioventricular nodal rhythm.

During the next few hours the heart rate rose to slightly over 40 per minute. At 7:10 P.M. she had two convulsive seizures, lasting two and three minutes, during which no pulse was obtained. At 9:00 P.M. she had a third seizure lasting one minute during which an electrocardiogram (Fig. 3) revealed atrial and ventricular standstill. An external electric cardiac pacemaker* was tested, was found to produce effective beats at 50 volts (Fig. 4A), and was then kept in emergency readiness. The atrioventricular nodal rhythm slowed progressively and was occasionally replaced by a slow idioventricular rhythm. (Figs. 4B and C.) Two more seizures occurred at 4:15 and 5:30 A.M.

* Manufactured by the Electrodyne Company, Norwood, Mass.

still. Following the clear definition by Parkinson, Papp and Evans [5], we restrict the term "Stokes-Adams attacks" to episodes of cardiac arrest that occur in patients with pre-existing A-V block of any degree. We recognize that strict interpretation of this definition may be difficult in borderline cases that involve vagal effects. Nevertheless, unless this restriction is carefully adhered to, "Stokes-Adams disease" becomes synonymous with any type of cardiac syncope and loses its historic meaning.

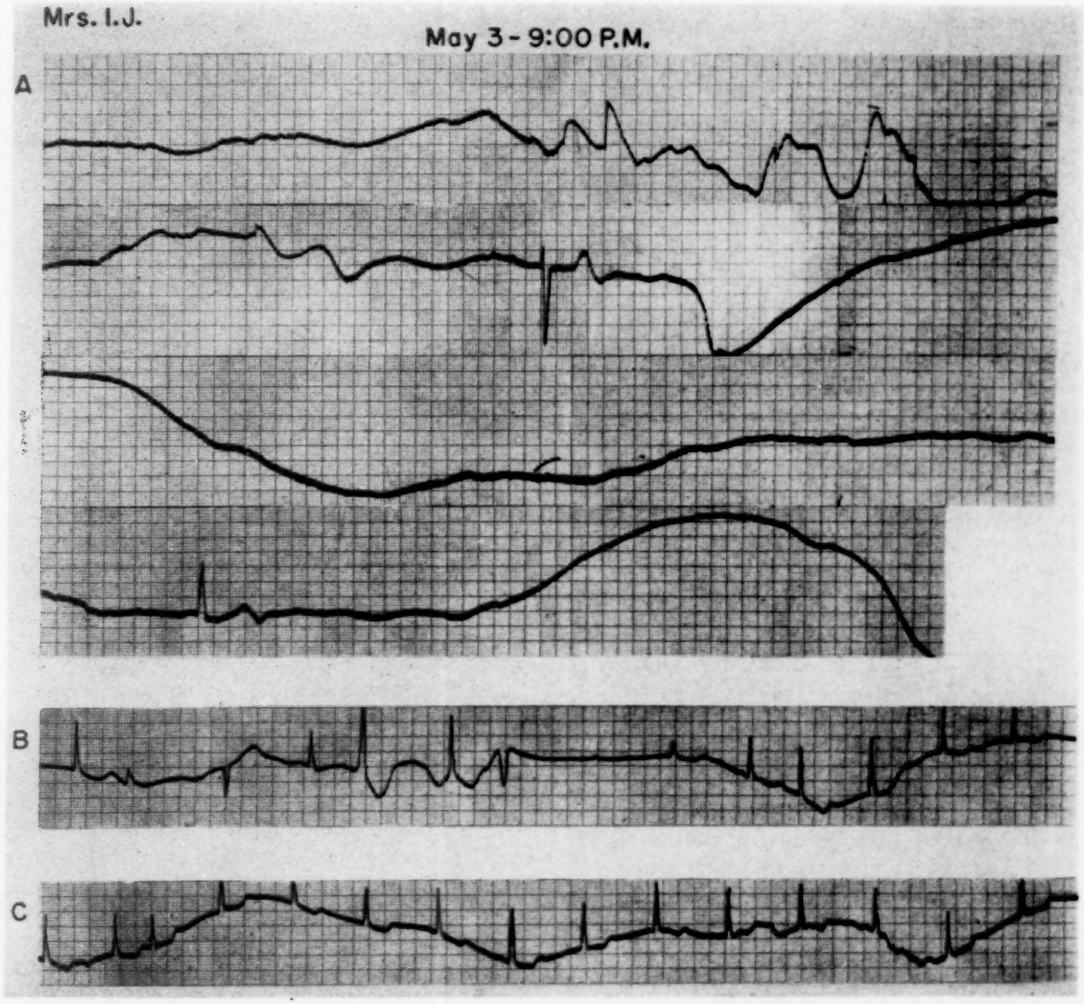


FIG. 3. A, continuous electrocardiogram (lead aVF) taken after onset of a seizure shows atrial and ventricular standstill for fifty-one seconds interrupted by 2 ventricular escape beats. The marked irregularity of the baseline was due to convulsive movements. B, an irregular rhythm has returned thirty-seven seconds later. C, after another thirty-seven seconds a more regular A-V nodal rhythm has returned.

from which she was immediately resuscitated by brief external electric stimulation of the heart. (Fig. 4D.)

Carotid sinus pressure slowed the nodal rate; 1 mg. of atropine sulfate was then given intravenously, and the A-V nodal rhythm accelerated promptly from 38 to 50 per minute. Thereafter atropine was administered subcutaneously every four hours; a definite acceleration followed the administration of 0.8 mg. but an unsatisfactory response was evident after the administration of 0.4 mg. (Fig. 1.) On May 5 at 10:00 A.M., two hours after administration of 0.4 mg. of atropine, a sinoatrial beat was noted for the first time since the tracing taken on admission. (Fig. 5A.) At 1:45 P.M., three hours after the administration of 0.8 mg. of atropine, uninterrupted sinoatrial rhythm was observed. (Fig. 5B.) As the effect of the atropine waned, depression of sinoatrial impulse formation was again observed in the form of sinus arrhythmia (Fig. 5C) and in the escape of lower supraventricular beats. (Figs. 5D and E.) With the administration of 0.8 mg. of atropine every four hours, sinoatrial rhythm reappeared and continued without interruption for twelve hours. Atrial fibrillation then occurred, lasted for forty-eight hours, and was followed by persistent sinoatrial rhythm. (Fig. 6.)

During the first twenty-four hours of hospitalization, 2,600 ml. of fluid containing 73 mEq. of potassium chloride were given intravenously. The potassium was given because of the evidence of digitalis intoxication, but it did not accelerate the heart rate or prevent seizures. On the morning of May 4 the serum potassium was 6.4 mEq./L.; serum sodium, 136 mEq.; chloride, 96 mEq.; carbon dioxide, 19 mEq.; and non-protein nitrogen, 53 mg. per cent. Only 15 ml. of urine were excreted during the first twenty-four hours.

On May 5 the temperature rose to 101°F., basal

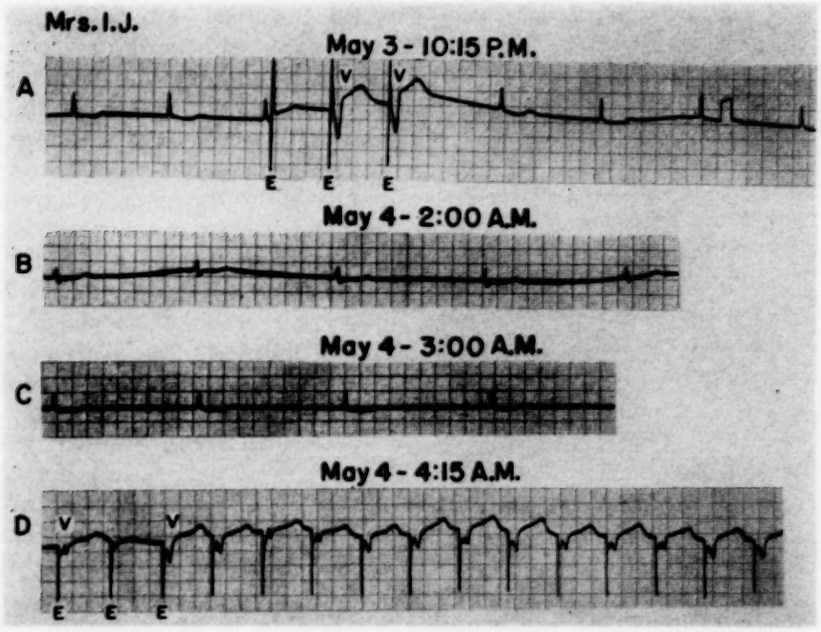


FIG. 4. (Lead II.) A, effective stimulation during A-V nodal rhythm. The first electric stimulus (E) is ineffective, presumably because it falls in the refractory period of the preceding beat. Without change in voltage, the next two stimuli evoke ventricular responses (V), which suppress an A-V nodal beat that would have occurred at this time. B, slow idioventricular rhythm; R-R = 1.86 seconds. C, slow A-V nodal rhythm; R-R = 1.93 seconds. D, termination of seizure by external electric stimulation. The second stimulus (E) just below threshold intensity is ineffective and does not evoke a ventricular response (V).

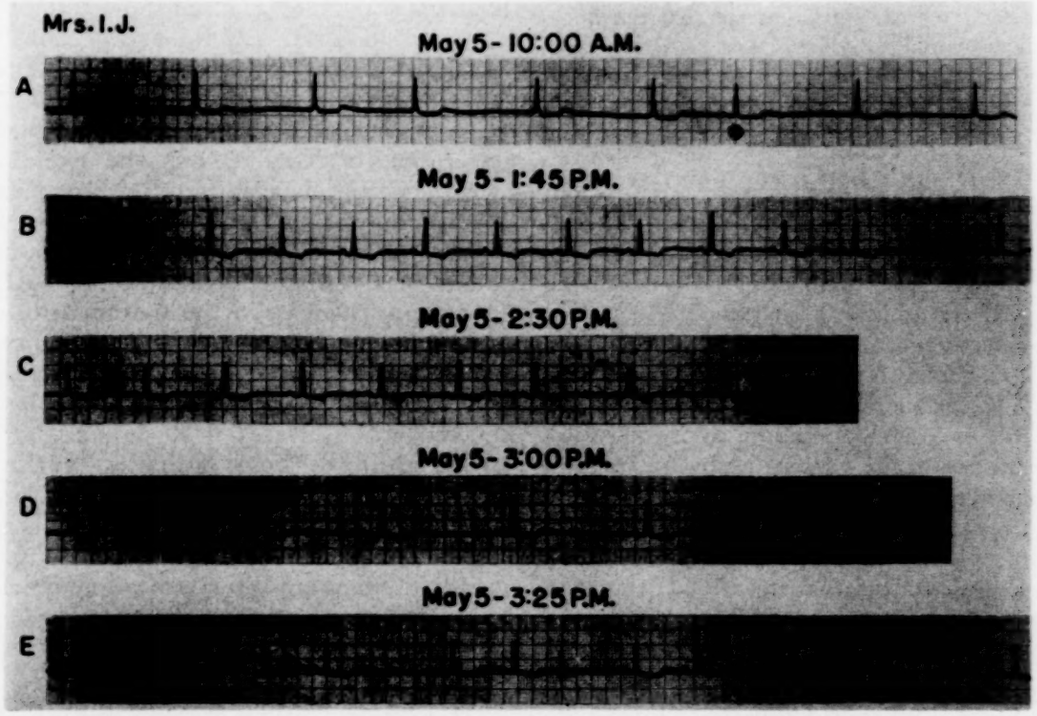


FIG. 5. (Lead II.) Dependence of sinoatrial activity on atropine (0.4 mg. at 8:00 A.M., 0.8 mg. at 11:00 A.M.). A, A-V nodal rhythm interrupted by a single sinoatrial beat (●). B, uninterrupted sinoatrial rhythm. C, sinus arrhythmia. D, slow sinoatrial rhythm interrupted irregularly by escape of lower supraventricular beats. E, bigeminy caused by alternation of supraventricular beats and sinoatrial beats. The short cycle before and the long cycle after each sinoatrial beat indicate alternating variation in sinoatrial rhythmicity.

rales were heard, and penicillin and streptomycin were given. The non-protein nitrogen was 73 mg. per cent; the potassium, 6.8 mEq. per cent; the sodium, 132 mEq.; the chloride, 97 mEq.; and the carbon dioxide, 19 mEq. The patient was anuric until the afternoon of May 5 when she voided 150 ml. This out-

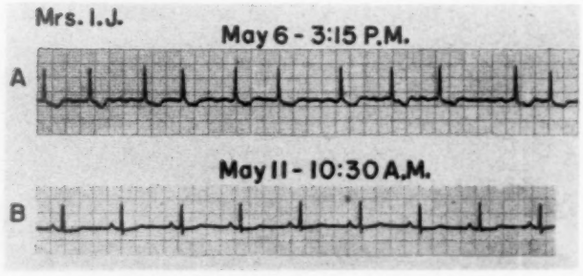


FIG. 6. (Lead II). A, atrial fibrillation. B, sinoatrial rhythm.

put occurred after the heart rate had been above 60 per minute for several hours. During the anuric period when the heart rates were low, the blood pressure ranged between 130/40 mm. Hg and 170/60 mm. Hg. When the heart rate was above 60 per minute, the blood pressure rose to 190/90 mm. Hg. The urinary output increased steadily and the serum electrolytes returned to normal within a few days. The fever disappeared, the lungs cleared, the non-protein nitrogen fell to 51 mg. per cent, and the patient was discharged on the seventeenth hospital day (May 20) in apparent good health.

COMMENTS

It is quite clear that the progressive depression of cardiac impulse formation in this patient culminating in ventricular standstill and syncope was due to digitalis. Sinoatrial block as observed here is well recognized as a characteristic although infrequent manifestation of digitalis intoxication. Characteristic gastrointestinal manifestations of digitalis toxicity were also present in the form of anorexia, nausea and vomiting. The occurrence of the various arrhythmias and their consistent temporal relationships to the doses of digitalis further suggested that digitalis was responsible for the cardiac syncope.

In this patient, on two occasions, external electric stimulation terminated ventricular standstill by producing effective beats. Thus the external cardiac pacemaker is effective in resuscitating patients from ventricular standstill due to digitalis therapy as well as from Stokes-Adams attacks, reflex vagal standstill, unexpected arrest in the operating room and from standstill due to procaine amide.

Recently we have successfully terminated ventricular tachycardia and ventricular fibrillation in man by external electric countershock [*6*]. It is therefore possible to resuscitate patients from the two most threatening toxic effects of digitalis, ventricular fibrillation and ventricular standstill, by the external application of the appropriate electric current. During digitalis therapy, any manifestation of ectopic activity or depression of impulse formation forewarns of potentially lethal cardiac arrhythmia and necessitates omission of the drug and careful observation. With progression of cardiac toxicity, some type of electrocardiographic monitoring is necessary to permit immediate recognition of a cardiac emergency and determination of the nature of the arrhythmia. In addition, an external defibrillator and an external cardiac pacemaker should be in emergency readiness.

Atropine was clearly of value in this case. Adequate doses on May 4 accelerated the A-V nodal rate and thereby probably prevented further episodes of syncope. With subsequent reduction in the dosage of atropine the A-V nodal rate fell again. With increased dosage on May 5 the A-V nodal rate rose and sinoatrial activity reappeared. A detailed analysis showed the dependence of sinoatrial activity at this time on the administration of atropine. (Fig. 5.) The reappearance of the sinoatrial pacemaker on May 5, in contrast to the more marked A-V nodal acceleration of May 4, may be explained by waning of the depression of the sinoatrial node by digitalis.

The administration of potassium, on the other hand, was without apparent benefit. Although potassium is useful in the treatment of ectopic activity due to digitalis [*7*], it is not indicated for depressed impulse formation and may even be harmful by depressing ventricular pacemakers [*8*].

An additional point of interest was the renal problem. The persistent oliguria and azotemia were of great concern. They were probably associated with diminished cardiac output as a result of the slow heart rate and the relative hypotension.

SUMMARY

A case of cardiac syncope due to digitalis intoxication is reported in which episodes of cardiac standstill were terminated by external electric stimulation of the heart. Atropine was of value in accelerating atrioventricular nodal

rhythmicity and in hastening the return of sinoatrial activity, thereby probably preventing further seizures.

Acknowledgments: We wish to thank Drs. George E. Altman and J. E. F. Riseman for their helpfulness and for their permission to report this case, and Mrs. Beverly Fordyce for her technical assistance.

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Post-transfusion Thrombocytopenic Purpura*

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SEVERE thrombocytopenic purpura is known to follow the administration of blood from donors previously sensitized by transfusion or pregnancy [*8*], from donors with drug sensitivities if the recipient simultaneously receives the offending drug [*2*] and from donors with idiopathic thrombocytopenic purpura [*9*]. The case presented here is that of a patient in whom thrombocytopenic purpura developed following surgery and the transfusion of blood from a donor who had never himself received blood and who was not suffering from drug sensitivity or from idiopathic thrombocytopenic purpura.

CASE REPORT

The patient, S. C. (349752), a fifty-nine year old Chinese-American housewife, entered the surgical service of the Stanford University Hospital on February 19, 1956, because of recurrent attacks of bilateral flank pain over a period of six or seven years. Two years before she was told that she had kidney stones. She was first seen in the Stanford Out-patient Clinic in January 1956, where studies revealed a large staghorn calculus in the left kidney. Blood urea, calcium and phosphorus determinations at this time were within normal limits. Physical examination on admission was noteworthy only for an arterial pressure of 180/100 mm. Hg. Laboratory studies made on admission revealed the following: hemoglobin, 10.7 gm. per 100 cc.; packed red cell volume, 35 per cent; white blood cell count, 4,000 per cu. mm., with a normal differential and an adequate number of platelets on the blood film; a negative urinalysis and a blood type of AB, Rh_0 positive.

Because of the anemia and the anticipated surgical blood loss, the patient received one unit of blood on February 19, 1956, without reaction. The next day the staghorn calculus in the left kidney was removed and the patient received one unit of blood during the procedure and another a little later. Shortly thereafter hypotension developed, the wound bled, and the patient complained of sharp substernal pain and pain in the neck. Another unit of blood was started and the systolic blood pressure maintained between 110 and 120 mm. Hg. On the following day she continued to have pain in the chest and the question of myocardial infarction arose, but the electrocardiogram failed to confirm this.

She continued to have wound bleeding and purpura developed around the site of the incision. There was also quite marked hematuria. The white blood cell count was 8,100 per cu. mm., packed red cell volume was 32 per cent, and the platelets on the blood film were noted to be greatly decreased. Because of continued bleeding and anemia, she was given two more units of blood. On February 22 the patient continued to have hematuria and oozing from her wound. In addition many petechiae were noted at the site of application of the blood pressure cuff. The white blood cell count was 7,000 per cu. mm.; packed red cell volume 32 per cent; platelet count, 40,000 per cu. mm.; bleeding time, eleven and a half minutes (Quick); clotting time, eight minutes (Lee-White); and there was only slight clot retraction after three hours. The Rumpel-Leede test was positive. The patient was given two more units of blood, and a course of intravenous hydrocortisone hemisuccinate, 200 mg. daily, was begun. On February 23 the patient showed signs of improvement. The white blood cell count was 5,800 per cu. mm.; packed red cell volume, 49 per cent; red platelet count, 150,000 per cu. mm. Two days later she was started on a regimen of cortisone 50 mg. daily. On March 4 the patient was discharged much improved. Her platelet count at the time of discharge was 220,000 per cu. mm.

ADDITIONAL STUDIES

Because of the very sudden development of thrombocytopenia and purpura, an investigation of blood from donors for platelet antibodies was carried out. First, all the blood from donors was rechecked for red cell incompatibility. All donors were type AB, RH_0 positive. Direct and indirect Coombs' tests were carried out on all blood from the donors and from the recipient. No red cell antibodies were found. Prior to the

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development of the thrombocytopenic reaction the patient had received three units of blood and of these only two were given immediately before the reaction. The two donors whose blood had been given just prior to the reaction were examined. Donor No. MB 0358 had a normal history and physical examination, a red blood cell count of 5.51 million per cu mm., and a platelet count of 240,000 per cu. mm. Donor No. 3803 had a past history of meningoencephalitis and at present is undergoing treatment for Boeck's sarcoid. His physical examination was within normal limits; the red blood cell count was 5.02 million per cu. mm., and the platelet count was 235,000 per cu. mm. The former donor had given blood six times without a history of recipient reaction; the latter had given blood only on this one occasion. Neither had at any time in the past received blood.

Platelet suspensions and serums were prepared by the method of Gurevitch and Nelken [*7*]. The results of the tests revealed that the serum from donor No. 3803 would cause agglutination of the patient's platelets and that from donor No. MB 0358 would not. With platelets from five normal healthy volunteers it was found that the serum from donor No. 3803 caused agglutination in every case and that from donor No. MB 0358 caused no agglutination in any case. Positive control serum was obtained from a patient with idiopathic thrombocytopenic purpura.

COMMENTS

The first immunologic experiments with platelets date back to 1905 when Marino [*14*] demonstrated the heterologous property of human platelets by production of platelet antiserums in experimental animals. Two years following this Cole [*3*] elaborated on these experiments and described the agglutination of platelets *in vitro* by antiserums. He also noted that lysis of platelets occurred if the antiserum used was not heat-inactivated before incubation with the platelet suspension. In 1914 Ledingham, and Ledingham and Bedson [*11,12*] described the development of thrombocytopenic purpura in animals following the injection of platelet antiserum. They were impressed with the massive bleeding tendencies and fatalities following injection. Subsequent experiments [*17,27*] have borne out these findings. In a rather detailed report Tocantins [*27*] in 1936 described experimental thrombocytopenic purpura in dogs following the intraperitoneal injection of platelet antiserum. He noted that there was a fall in platelets to very low levels within three to five hours following the injection, accompanied by the appearance of purpura and gastrointestinal bleeding. This was followed by a return of platelet levels to normal in three to five days and the appearance of macrothrombocytes in the peripheral blood. He also observed the presence of clumped platelets and white cells in wet preparations of blood taken from the animals after the injection of the platelet antiserum.

That thrombocytopenic purpura in man might be due to some immunologic factor had been suggested [*19,26,28*], and Evans et al. [*6*] in 1951 presented *in vitro* evidence of an isoimmune antibody in the serums of patients with idiopathic thrombocytopenic purpura. They also suggested that neonatal thrombocytopenic purpura might be due to placental transmission of this iso-antibody. Shortly after this Harrington et al. [*9*] demonstrated that serums from patients with idiopathic thrombocytopenic purpura contained *in vitro* iso-agglutinins for normal human platelets, and would produce fulminating thrombocytopenic purpura when injected into normal human volunteers.

There are numerous reports in the literature of drug-induced thrombocytopenic reactions [*1,2,16,25*]. *In vitro* agglutination of platelets incubated with the offending drugs and serums from sensitive patients has been demonstrated. It has been postulated that in these reactions an abnormal platelet-antigen complex exists. Steinkamp et al. [*25*] demonstrated the development of thrombocytopenic purpura in a normal human volunteer when injection of serum from a patient sensitive to quinine was followed by the ingestion of this drug. Mild thrombocytopenic reactions without the development of purpura following the transfusion of compatible blood have been described [*5,13,24*]. These reactions occur in as high as 80 per cent of normal human volunteers receiving normal compatible plasma [*23*], but iso-agglutinins are demonstrable in only 6 to 14 per cent of normal serums [*10,20*]. Platelet types both independent of and similar to the major blood groups have been described [*4,7,8,10,15,21–24*].

Thrombocytopenic reactions of an immunologic type are known to occur in persons who have received numerous transfusions over a prolonged period, and the development of an isoantibody for platelets has been shown to occur in pregnancy in maternal blood [*6,8,10,19–23,26,28*].

In the case presented here it would appear that platelet agglutinins in the blood of a donor were responsible for the development of thrombocytopenic purpura. On further investigation it was found that the donor in whose blood these antibodies could be demonstrated had Boeck's sarcoid. Studies of the immunologic reactivity of patients with sarcoidosis have shown that there is an increased ability to manufacture circulating antibodies [*18*]. Because of this apparent serologic hyper-reactivity in persons with sarcoidosis, it is doubtful that they should be allowed to donate blood, even in the absence of obvious blood abnormality.

SUMMARY

1. A case of post-transfusion thrombocytopenic purpura is presented. The serum of a donor with sarcoidosis and without previous exogenous sensitization was shown to contain platelet agglutinins.

2. Immunologic mechanisms involved in the pathogenesis of thrombocytopenic purpura are discussed and the serologic hyper-reactivity of patients with sarcoid cited.

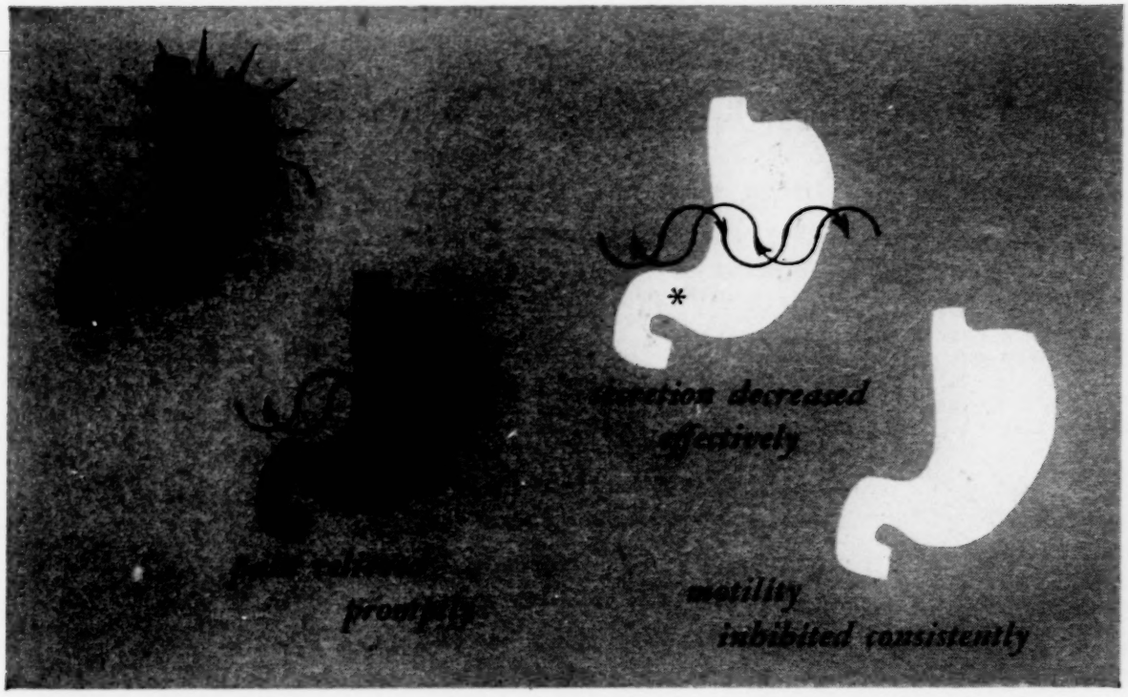
3. Sudden occurrence of purpura in a patient receiving apparently compatible blood should lead one to suspect the presence of platelet antibodies in the blood from the donor.

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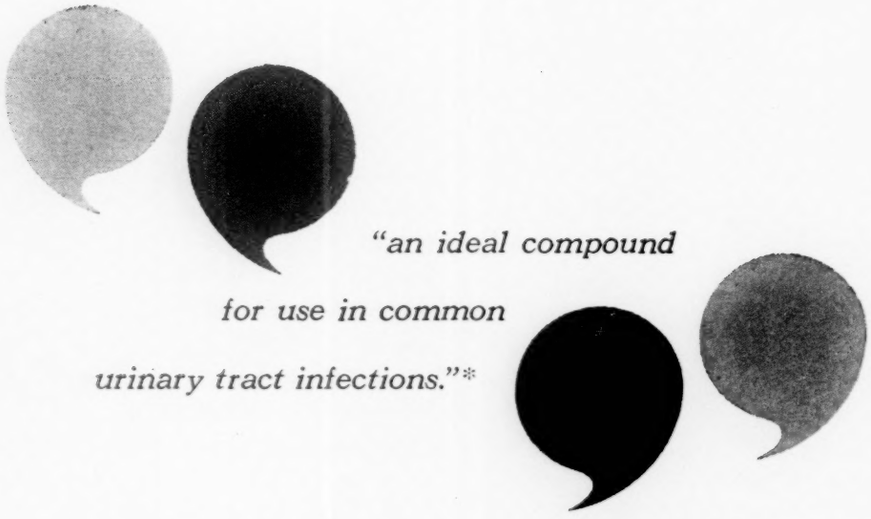
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Satisfactory results were obtained in over 96 per cent of cases in a series of 267 patients who received estrogen and androgen as combined in "Premarin" with Methyltestosterone. Therapy was started as soon as possible after delivery. No untoward side effects were noted. In addition, the absence of mental depression in the puerperium was considered of notable importance.*

*Fiskio, P. W.: GP *11*:70 (May) 1955.

"PREMARIN®" with METHYLTESTOSTERONE

for combined estrogen-androgen therapy

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for the depressed and regressed

selective increase in psychic energy

MARSILID

(iproniazid) Roche

In both mild and severe depression, Marsilid can restore a sense of healthy well-being, with renewed vigor, activity and interests. Patients with acute depression refractory to shock treatment have shown a heartening response to Marsilid. Even "burned out" psychotics, untouched by any other therapy, have become more alert, responsive and sociable.

As a psychic energizer, Marsilid is truly unique. It provides continuous mood improvement with gradually reduced dosage. Patients do not develop resistance to its normalizing effect; there is no tachyphylaxis. Marsilid does not elevate blood pressure . . . does not decrease but usually stimulates appetite.

In mild depression, improvement with Marsilid is usually evident within a week or two. In severe depressive states of hospitalized psychotics, a month or more may be required for apparent response . . . but Marsilid often leads to complete remission, obviating the need for shock therapy.

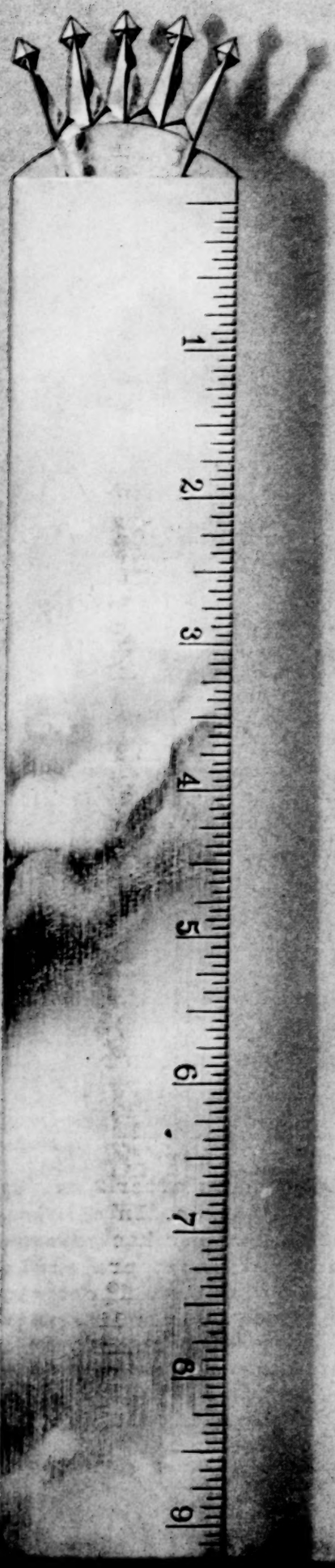
Note: Marsilid is contraindicated in patients who are agitated, overactive or overstimulated, or in those with a history of renal or hepatic disease.

For complete references and information concerning dosage, indications and contraindications, write V. D. Mattia, Jr., M. D., Director of Medical Information, Roche Laboratories, Division of Hoffmann-La Roche Inc, Nutley 10, N. J.

MARSILID® PHOSPHATE – brand of iproniazid phosphate

Supplied in scored tablets of 50 mg (yellow), 25 mg (orange), and 10 mg (pink)

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GOLDEN RULE
FOR COUGHS

A
little
calcidrine
goes
a long
way
to treat
a bad
cough

calcidrine®

syrup



each 30 cc. represents:

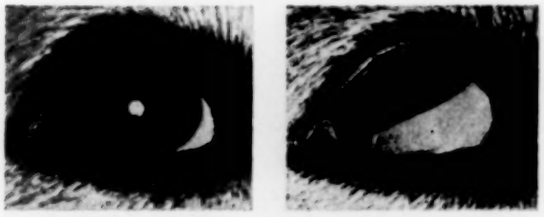
Dihydrocodeinone Bitartrate	10 mg. (⅙ gr.)
Nembutal® Sodium	25 mg. (⅜ gr.)
Ephedrine Hydrochloride	25 mg. (⅜ gr.)
Calcium Iodide, anhydrous	910 mg. (14 grs.)

®Nembutal—Pentobarbital, Abbott

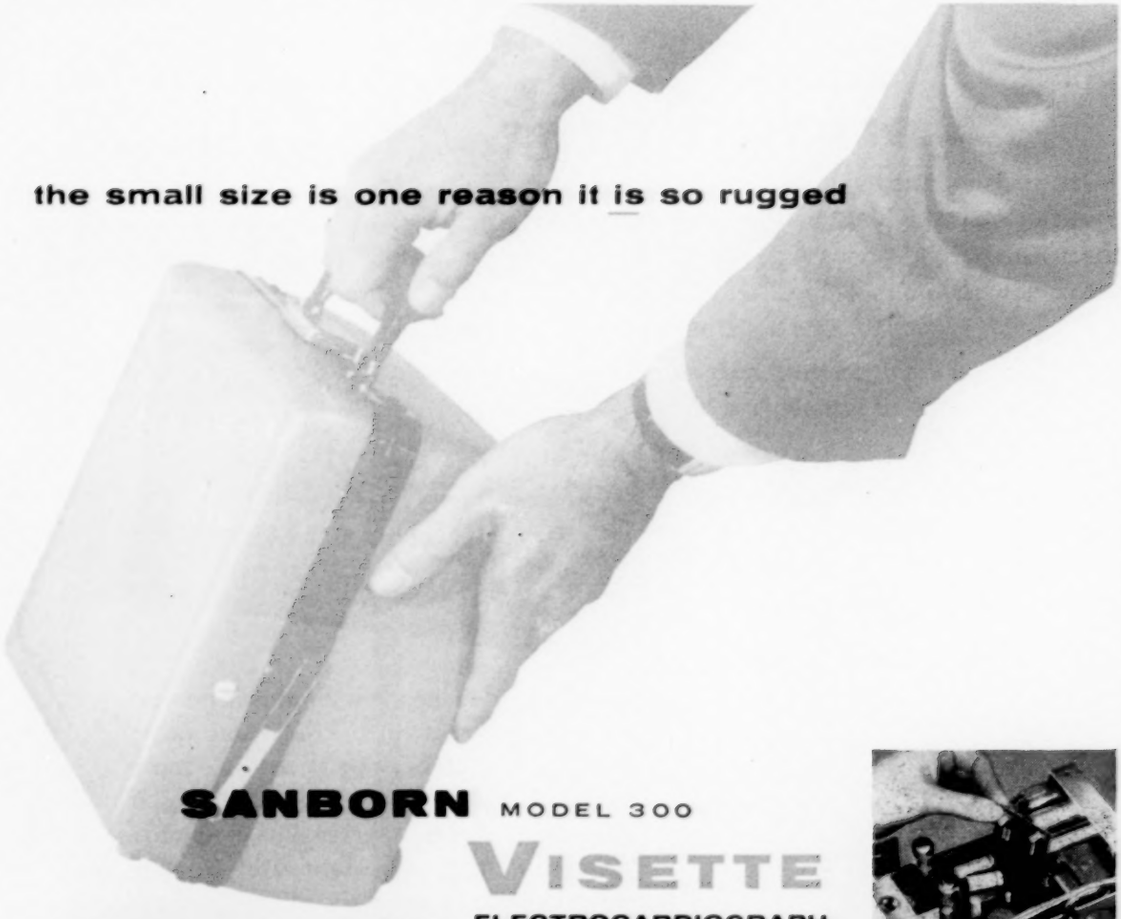
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dramatic antihypertensive action*



*Nictitating membrane of the dog, before and 8 hours after 2 mg./kg. Ecolid, shows dramatic ganglionic blocking action. In clinical medicine, this newer, longer acting ganglionic blocker has reversed the course of severe hypertension in many patients, prolonging their lives. Please become completely familiar with Ecolid® chloride (chlorisondamine chloride CIBA) before using it. Complete literature available from Medical Service Division, **C I B A** Summit, N. J.



the small size is one reason it is so rugged

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ELECTROCARDIOGRAPH

modern components, construction give greater durability



18 lbs. TRANSISTORIZED $625 del.



An informative four-page folder describes and pictures all major characteristics of the new Model 300 Visette electrocardiograph. Copies available on request.

The transistors, printed wiring panels and smaller galvanometer that help make the new 18 pound VISETTE ecg the size of a brief case also make possible another — and equally important — advantage: *ruggedness*. Metal-encased transistors, most of them smaller than a pencil eraser, are used in place of many vacuum tubes in the Visette circuit; they can withstand extreme jolts, jars and vibration without damage. And instead of dozens of connections which would ordinarily be made with wire, conductive paths are *printed* on small, rigid phenolic panels. The Visette's direct-writing galvanometer, too, is designed for increased resistance to both physical and electrical hazards. The rigid metal frame and chassis, to which all units are anchored, is then housed in an outer case of high impact Royalite, reinforced with metal strips at points of greatest strain.

Here is *true* portability — a carefully designed combination of *light weight* (that every nurse and technician will appreciate); *small size* (that requires the same space on your desk as a letterhead); and *ruggedness*, that assures continued accuracy of operation after countless trips in your car, on hospital and house calls, wherever your Visette is required. Handy "companions" for the Visette include a protective vinyl Weather Cover, and a compact, attractive table for office use of the Visette.

You *can* take it with you — *with confidence.*

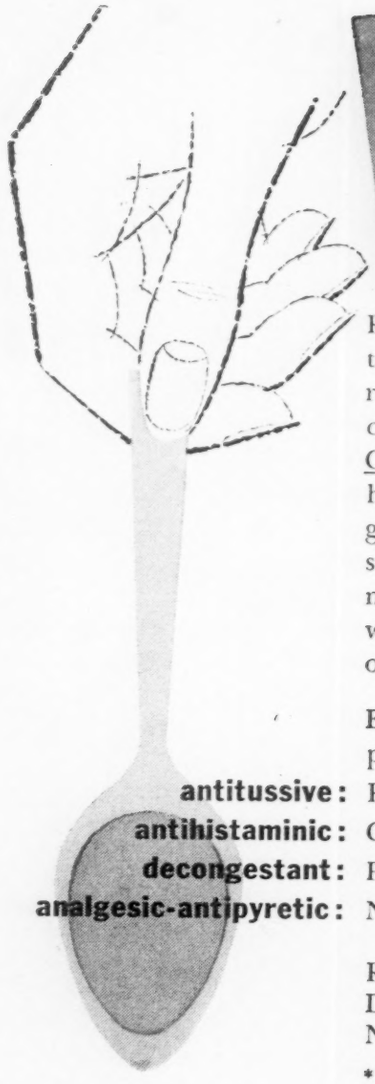
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Romilar CF brings new comfort and ease to your patients with colds and other respiratory disorders by providing more complete symptomatic control. Romilar CF syrup combines the benefits of an antihistaminic, a decongestant, and an analgesic-antipyretic with the effective cough suppressant action of Romilar Hydrobromide* — the non-narcotic cough specific with codeine's antitussive effect but without codeine's side effects.

Each teaspoonful (5 cc) of Romilar CF provides:

antitussive:	Romilar ® Hydrobromide* ..... 15 mg
antihistaminic:	Chlorpheniramine Maleate .....1.25 mg
decongestant:	Phenylephrine Hydrochloride... 5 mg
analgesic-antipyretic:	N-acetyl-p-aminophenol ..... 120 mg

ROCHE LABORATORIES
Division of Hoffmann-La Roche Inc
Nutley, New Jersey

*Brand of dextromethorphan hydrobromide

Life without Frenzy

He used to fuss and fume when traffic slowed him down. Now he relaxes—his pace of living has been "calmed down"—since his doctor prescribed

Butiserpine®

That's the tranquilizing-sedative-hypotensive effect BUTISERPINE has on tense, highstrung patients. Its *Butisol* component quickly induces a more reasonable, tranquil attitude. This gives the *reserpine* component a chance to build up to its maintenance tranquilizing effect.

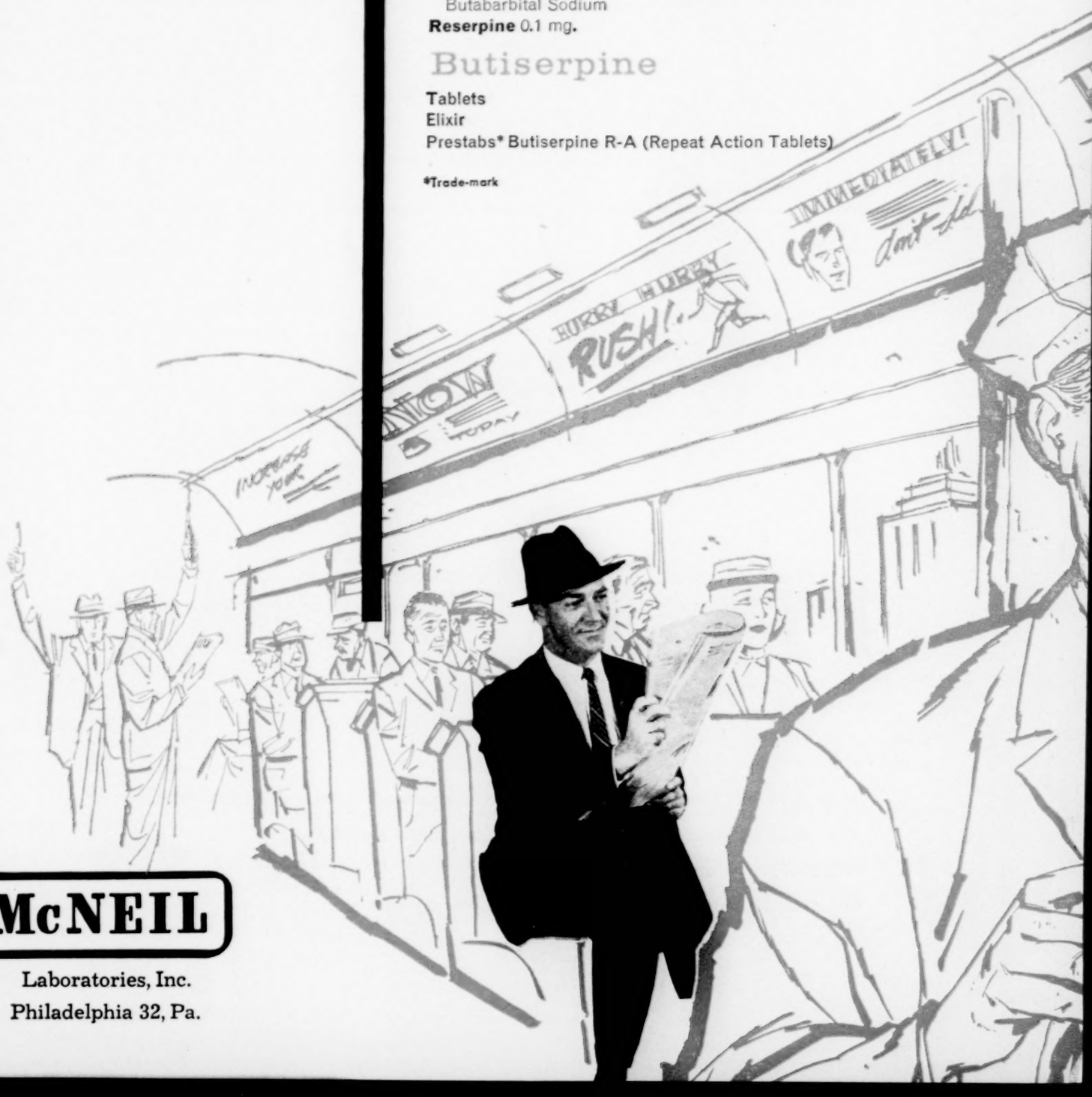
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BUTISOL SODIUM® 15 mg. (¼ gr.)
Butabarbital Sodium
Reserpine 0.1 mg.

Butiserpine

Tablets
Elixir
Prestabs* Butiserpine R-A (Repeat Action Tablets)

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MAALOX®, an efficient antacid suspension of magnesium-aluminum hydroxide gel;
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Phenaphen Plus is the physician-requested combination of **Phenaphen,** plus an antihistaminic and a nasal decongestant.

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each coated tablet contains: **Phenaphen**	
Phenacetin (3 gr.)	194.0 mg.
Acetylsalicylic Acid (2½ gr.)	162.0 mg.
Phenobarbital (¼ gr.)	16.2 mg.
Hyoscyamine Sulfate	0.031 mg.
plus	
Prophenpyridamine Maleate	12.5 mg.
Phenylephrine Hydrochloride	10.0 mg.

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when anxiety and tension "erupts" in the G. I. tract...

IN GASTRIC ULCER



PATHIBAMATE*

Meprobamate with PATHILON® Lederle

Combines Meprobamate (*400 mg.*) **the most widely prescribed tranquilizer . . . helps control the "emotional overlay" of gastric ulcer — without fear of barbiturate loginess, hangover or habituation . . .** *with* PATHILON (*25 mg.*) **the anticholinergic noted for its extremely low toxicity and high effectiveness in the treatment of many G.I. disorders.**

Dosage: **1 tablet t.i.d. at mealtime. 2 tablets at bedtime.** *Supplied:* Bottles of 100, 1,000.

*Trademark ®Registered Trademark for Tridihexethyl Iodide Lederle

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in the menopause and the pre- and postmenopausal syndrome

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What is a Sensible Breakfast?

The division of his day into periods for productive work, for play, and for sleep makes man fare best when his total daily food intake is distributed over three sensibly organized meals.

Since a high percentage of adolescents and adults forego or skimp breakfast, the physician might well point out the need for a sensible breakfast: a meal which provides energy for a morning of productive work, which allays hunger until the noon meal, which supplies an adequate share of the day's nutrient requirements, and which consists of inviting, easily digested foods.

A dish of oatmeal helps fulfill the requirements of such a breakfast: It provides readily available energy; it helps to allay hunger throughout the morning; it makes a notable contribution to the day's nutritional needs; it fits into virtually every breakfast, including most of those especially low in calories.*

Oatmeal is richer in protein than other whole-grain breakfast cereals. None are as high in thiamine as oatmeal. Also, oatmeal provides other B-complex vitamins. Its mineral content, especially of iron and phosphorus, rates it among the leaders.

Its delicious taste and easy digestibility further qualify oatmeal as an ideal "habit food" for a sensible breakfast.

Quaker Oats and Mother's Oats, the two brands of oatmeal offered by The Quaker Oats Company, are identical. Both brands are available in the Quick (cooks in one minute) and the Old-Fashioned varieties which are of equal nutrient value.

***WHEN THE DAY'S CALORIE ALLOWANCE IS**

1400 CALORIES OR LESS PER DAY	2400 CALORIES PER DAY	3000 CALORIES OR MORE PER DAY
Breakfast	**Breakfast**	**Breakfast**
Approximately 300 Calories	**Approximately 500 Calories**	**Approximately 700 Calories**
Orange juice, 4 oz.	Orange juice, 4 oz.	Orange juice, 4 oz.
Oatmeal, 1 oz. Skim milk, 4 oz. Sugar, 1 tsp.	Oatmeal, 1 oz. Milk, 4 oz. Sugar, 1 tsp.	Oatmeal, 1 oz. Milk, 4 oz. Sugar, 1 tsp.
Toast, 1 slice lightly buttered	One egg	Two eggs
†Coffee without cream or sugar	Toast, 2 slices with butter or jelly	Bacon, 2 strips
	†Coffee with cream and sugar	Toast, 2 slices with butter or jelly
†For children substitute 4 oz. skim milk		†Coffee with cream and sugar



The Quaker Oats Company

CHICAGO



A strong move in parkinsonism

COGENTIN®

METHANESULFONATE (BENZTROPINE METHANESULFONATE)

The distressing symptoms of parkinsonism—tremor, rigidity, contractures—can be controlled with COGENTIN. Because it is long-acting, one dose daily is sufficient.[1] Side effects are few.[1] A report on its 5-year use in 302 patients stated that COGENTIN is "...the most powerful orally given antispasmodic."[1] For optimum results, COGENTIN may be administered in conjunction with other antiparkinson drugs.

Reference: 1. J.A.M.A. 162:1031 (Nov. 10) 1956.

COGENTIN IS A TRADEMARK OF MERCK & CO., INC.

MSD

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DIVISION OF MERCK & CO., INC., PHILADELPHIA 1, PA.

INTRAVENOUS Compatible with common IV fluids. Stable for 24 hours in solution at room temperature. Average IV dose is 500 mg. given at 12 hour intervals. Vials of 100 mg., 250 mg., 500 mg.

INTRAMUSCULAR Used to start a patient on his regimen immediately, or for patients unable to take oral medication. Convenient, easy-to-use, ideally suited for administration in office or patient's home. Supplied in single dose vials of 100 mg., (no refrigeration required).

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Hydrochloride
Tetracycline HCl *Lederle*

THERAPEUTIC BLOOD LEVELS ACHIEVED IN MINUTES -- SUSTAINED FOR HOURS

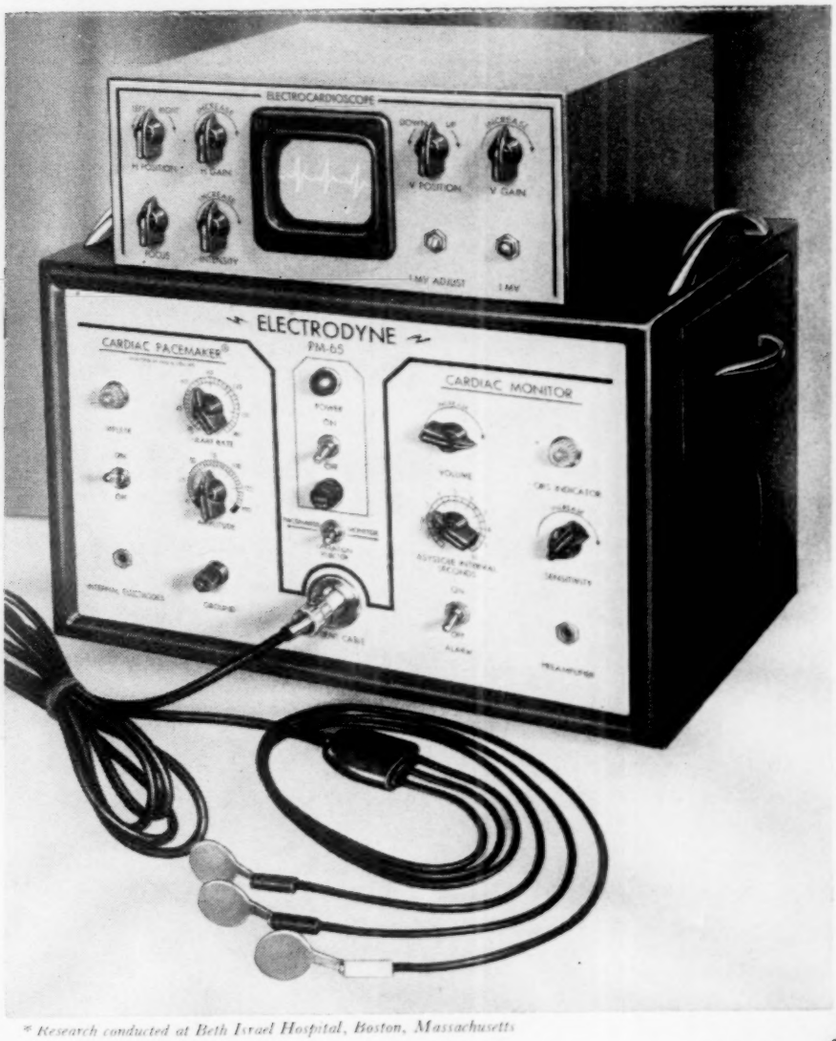
Many physicians advantageously use the parenteral forms of ACHROMYCIN in establishing immediate, effective antibiotic concentrations. With ACHROMYCIN you can expect prompt control, with minimal side effects, over a wide variety of infections - reasons why ACHROMYCIN is one of today's foremost antibiotics.

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*Reg. U. S. Pat. Off.

ELECTRODYNE PM-65 with *Electrocardioscope**

**optional*



A PROVEN INSTRUMENT THAT:

- Detects and treats cardiac arrest automatically.
- Provides continuous visual display of electrocardiogram.
- Provides immediate recognition of any cardiac arrhythmia.

The 3 flat E. C. G. disk electrodes held on chest by rubber strap, afford simple, fast, external hookup.



* *Research conducted at Beth Israel Hospital, Boston, Massachusetts*

Your Inquiries for Technical Information, Literature, and Prices Invited...

With the addition of the new Electrocardioscope, the Electrodyne PM-65 boasts a refinement that is unlike any other instrument of its kind available today. The PM-65 with scope now provides a continuous visual display of the electrocardiogram and immediate recognition of any cardiac arrhythmia.

As you know, the Electrodyne PM-65 is a combination of two proven instruments — the reliable Cardiac Monitor and the well documented Cardiac Pacemaker (developed in conjunction with Paul M. Zoll, M. D.). When attached to the patient it will instantly signal cardiac arrest and automatically provide effective external stimulation to the dormant heart at the very onset of cardiac arrest.

Other important Electrodyne instruments are: The Cardiac Pacemaker, the Cardiac Defibrillator, the Cardiac Alarm, the *External* Defibrillator and combinations of these units.

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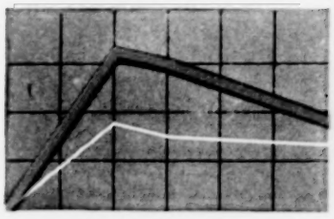
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capsules—given orally, produce "markedly higher serum concentrations than those obtained with tetracycline hydrochloride."[1]

Therapy with activated Tetracyn V thus provides a higher, faster activity level of tetracycline, established as outstanding in effectiveness and safety among broad-spectrum antibiotics.

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ACTIVATED TETRACYCLINE THERAPY FOR HIGHER, FASTER BLOOD LEVELS PROVIDES POTENT, PROMPT, PROLONGED CONTROL OF TETRACYCLINE-SUSCEPTIBLE INFECTIONS

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homogenized syrup

Orange-flavored, specially homogenized liquid preparation of activated tetracycline assures faster, higher levels of broad-spectrum therapy and assures acceptance by patients of all ages.

INFLUENZA patients and those with minor respiratory tract infections can get prompt symptomatic relief and protection or treatment of secondary bacterial complications with TETRACYDIN® Tablets (tetracycline-analgesic-antihistamine).

1. Welch, H.; Lewis, C. N.; Staffa, A. W., and Wright, W. W.: Antibiotic Med. & Clin. Therapy 4:215 (April) 1957.

Pfizer

PFIZER LABORATORIES, *Division, Chas. Pfizer & Co., Inc.*, Brooklyn 6, N. Y.
WORLD LEADER IN ANTIBIOTIC DEVELOPMENT AND PRODUCTION

for certain disorders of menstruation and pregnancy

TRULY EFFECTIVE PROGESTATIONAL THERAPY **BY MOUTH**

NORLUTIN™

(norethindrone, Parke-Davis)

oral progestogen
with
unexcelled potency
and
unsurpassed efficacy

Now, with small oral doses of this new and distinctive progestogen, you can produce the clinical effects of injected progesterone. In amenorrheic women for example, "As little as 50 mg. of [NORLUTIN] administered in divided doses over a five-day period was sufficient to induce withdrawal bleeding."[1]

CASE SUMMARY[2]

Amenorrhea of 4 years' duration in a 24-year-old married woman. A course of 10 mg. NORLUTIN twice daily for 5 days was followed after 3 days by menses lasting about 5 days. Since no spontaneous menstruation occurred during the following 35 days, she was given another course of treatment with NORLUTIN, 10 mg. twice daily for 5 days. This was followed by menses.

When this patient was given ethisterone, 40 mg. twice daily for 5 days, no bleeding had ensued when she was seen 41 days later.

INDICATIONS FOR NORLUTIN: conditions involving deficiency of progestogen such as primary and secondary amenorrhea, menstrual irregularity, functional uterine bleeding, endocrine infertility, habitual abortion, threatened abortion, premenstrual tension, and dysmenorrhea.

PACKAGING: 5-mg. scored tablets (C. T. No. 882), bottles of 30.

REFERENCES: (1) Greenblatt, R. B.: *J. Clin. Endocrinol.* 16:869, 1956. (2) Hertz, R.; Waite, J. H., & Thomas, L. B.: *Proc. Soc. Exper. Biol. & Med.* 91:418, 1956.

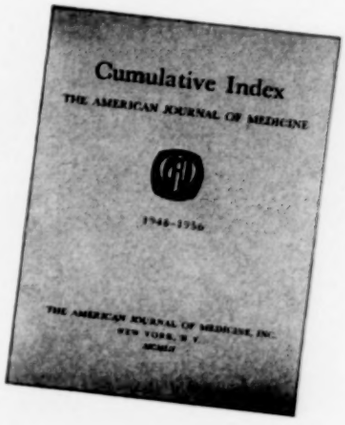
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when anxiety and tension "erupts" in the G. I. tract...

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Combines Meprobamate (*400 mg.*) the most widely prescribed tranquilizer . . . helps control the "emotional overlay" of duodenal ulcer — without fear of barbiturate loginess, hangover or habituation . . . *with* PATHILON (*25 mg.*) the anticholinergic noted for its extremely low toxicity and high effectiveness in the treatment of many G.I. disorders.

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It's Percodan®—relieves pain in *5 to 15 minutes*, with a single dose lasting 6 hours or longer.

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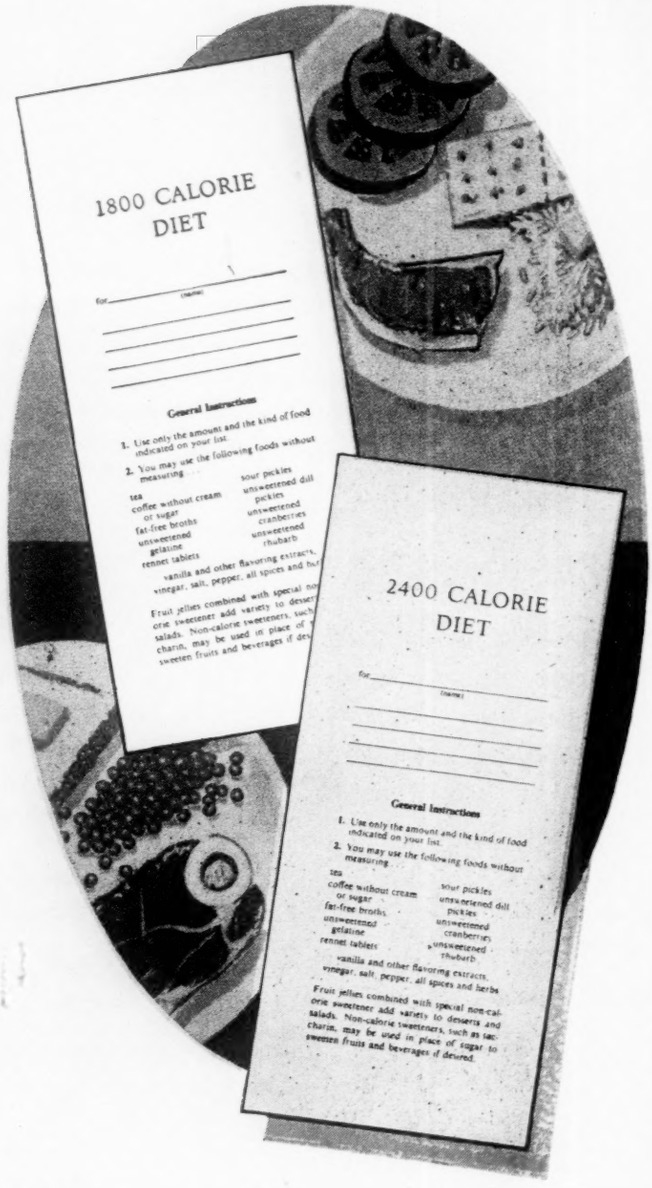
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Automatically measured-dose aerosol medications. In spillproof, leakproof, shatterproof, vest-pocket size dispensers. Also available in Medihaler-Phen™ (phenylephrine-phenylpropanolamine-hydrocortisone-neomycin) for prompt, lasting relief of nasal congestion.

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4. Paragraphs 2 and 3 include, in cases where the stockholder or security holder appears upon the books of the company as trustee or in any other fiduciary relation, the name of the person or corporation for whom such trustee is acting; also the statements in the two paragraphs show the affiant's full knowledge and belief as to the circumstances and conditions under which stockholders and security holders who do not appear upon the books of the company as trustees, hold stock and securities in a capacity other than that of a bona fide owner.

5. The average number of copies of each issue of this publication sold or distributed, through the mails or otherwise, to paid subscribers during the 12 months preceding the date shown above was:

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M. T. WISOTZKEY, President

Sworn to and subscribed before me this 9th day of September, 1957.

ROSE V. CELENTANO
Notary Public

[SEAL]

(My commission expires March 30, 1958.)



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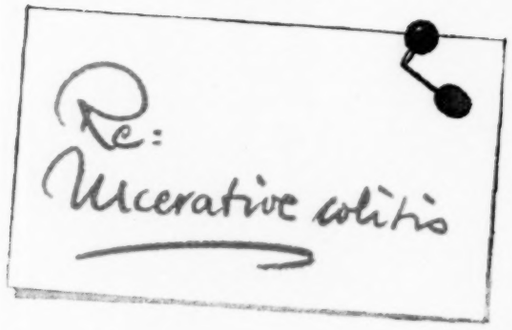
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1. BARGEN, J. A.: "Present Status of Hormonal and Drug Therapy of Ulcerative Colitis", South. M. J. *48*: 192 (Feb.) 1955.
2. BARGEN, J. A. and KENNEDY, R. L. J.: "Chronic Ulcerative Colitis in Children", Postgrad. Med. *17*: 127 (Feb.) 1955.
3. MORRISON, L. M.: "Response of Ulcerative Colitis to Therapy with Salicylazosulfapyridine", J. A. M. A. *151*: 366 (Jan. 31) 1953.

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1. Smith, R. T.: M. Clin. North America, March 1957. 2. Smith, R. T.: New York Med. 5:16, 1952.
3. Lehrer, H. W. et al.: Northwest Med. 75:1249, 1955.

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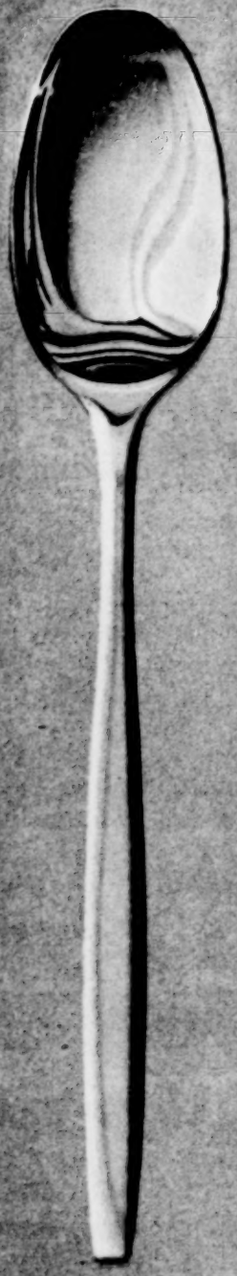
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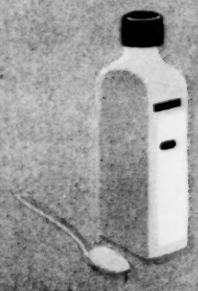


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Urticaria and angioneurotic edema	3	1	1	1		Dizzy (1)
Allergic dermatitis	2		1	1		Slight Drowsiness (2)
Bronchial asthma	1		1			
Pruritus	1		1			
Total	37	15	13	7	2	Drowsiness (5) Dizzy (1) 16.2%

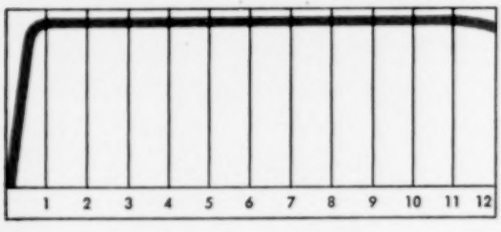
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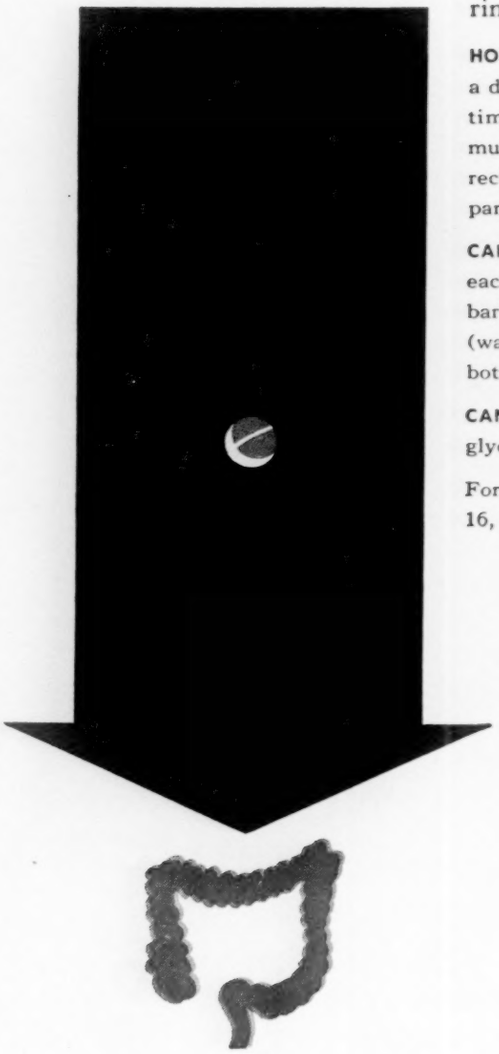
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1. LaBarbera, J. F.: Med. Rec. & Ann. *50*:242, 1956.
2. Ledbetter, P. V., and Morrow, E. J.: J. Am. Geriatrics Soc. *3*:172 (March) 1955. 3. Wilkins, R. W.: Am. J. Med. *17*:703 (Nov.) 1954.

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